(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64692 A1

(51) International Patent Classification[7]: C07F 9/58, C07D 213/65, 213/66, A61K 31/44, 31/675

(21) International Application Number: PCT/CA01/00265

(22) International Filing Date: 28 February 2001 (28.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/185,899 29 February 2000 (29.02.2000) US

(71) Applicant: MEDICURE INTERNATIONAL INC. [CA/CA]; Unit 24, 62 Scurfield Boulevard, Winnipeg, Manitoba R3Y 1M5 (CA).

(72) Inventor: HAQUE, Wasimul; 4832 17th Avenue, Edmonton, Alberta T6L 2Y7 (CA).

(74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc, Stock Exchange Tower, Suite 3400, P.O. Box 242, 800 Place Victoria, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/64692 A1

(54) Title: CARDIOPROTECTIVE PHOSPHONATES AND MALONATES

(57) Abstract: The present invention provides for pyrodoxine phosphonate analogues such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)alkylphosphonates, and (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)azaalkylphosphonates) and to pyridoxine malonates analogues, such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonates), pharmaceutical compositions, and methods for treatment of cardiovascular and related diseases, and diabetes mellitus and related diseases.

CARDIOPROTECTIVE PHOSPHONATES AND MALONATES

FIELD OF THE INVENTION

This invention relates to pyridoxine phosphonate analogues, to pyridoxine malonate analogues, to their preparation, to pharmaceutical compositions thereof, and to treatments for cardiovascular and related diseases, for example, hypertrophy, hypertension, congestive heart failure, myocardial ischemia, arrhythmia, heart failure subsequent to myocardial infarction, myocardial infarction, ischemia reperfusion injury, and diseases that arise from thrombotic and prothrombotic states in which the coagulation cascade is activated; and treatments for diabetes mellitus and related diseases, for example, hyperinsulinemia, diabetes-induced hypertension, obesity, insulin resistance. and damage to blood vessels, eyes, kidneys. nerves, autonomic nervous system. skin connective tissue, or immune system.

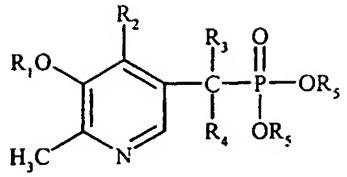
BACKGROUND

Pyridoxal-5'-phosphate (PLP), an end product of vitamin B_6 metabolism, plays a vital role in mammalian health. In previous patents (US 6,051,587 and US 6,043,259, herein incorporated by reference) the role of pyridoxal-5'-phosphate, and its precursors pyridoxal and pyridoxine (vitamin B_6), in mediating cardiovascular health and in treating cardiovascular related diseases is disclosed.

The major degradation pathway for pyridoxal-5'-phosphate *in vivo* is the conversion to pyridoxal, catalysed by alkaline phosphatase. Thus, there is a need to identify and administer drugs that are functionally similar to pyridoxal-5'-phosphate such as pyridoxine phosphonate analogues or pyridoxine malonate analogues, that elicit similar or enhanced cardiovascular benefits, and that beneficially affect PLP-related conditions, but are stable to degradation by phosphatase.

SUMMARY OF THE INVENTION

The present invention provides for pyridoxine phosphonate analogues and to pyridoxine malonates. In one aspect, the present invention includes a compound of formula I:



I

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3, –CO_2R_6 in which R_6 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

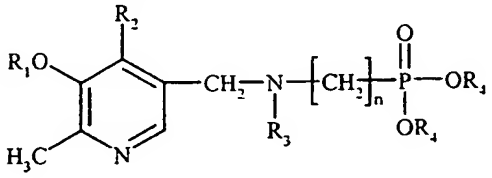
R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy, alkylcarbonyloxy, alkylamino or arylamino; or

R_3 and R_4 are halo; and

R_5 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_7 in which R_7 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, the present invention includes a compound of formula II:



II

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_5 in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen, alkyl, aryl, or aralkyl;

R_4 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_6 in which R_6 is

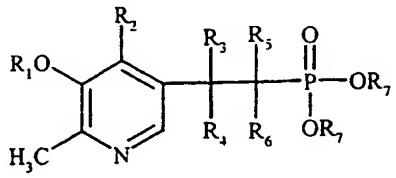
hydrogen, alkyl, aryl, or aralkyl; and

n is 1 to 6;

or a pharmaceutically acceptable acid addition salt thereof.

.

In another aspect, the present invention includes a compound of formula III:



III

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_8 in which R_8 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy or alkylcarbonyloxy; or

R_3 and R_4 can be taken together to form =O;

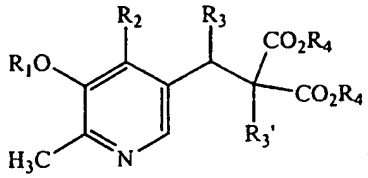
R_5 and R_6 are hydrogen; or

R_5 and R_6 are halo; and

R_7 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_8 in which R_8 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, the present invention includes a compound of formula IV:



IV

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_5 in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is $-CH_2.O$-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 and R_3' are independently hydrogen or halo; or

R_3 and R_3' taken together constitute a second covalent bond between the carbons to which they are substituent; and

R_4 is hydrogen or alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, the invention is directed to pharmaceutical compositions that include a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound of formula I, II, III or IV.

In another aspect, the invention is directed to a method of treating cardiovascular and related diseases, for example, hypertension, hypertrophy, arrhythmia, congestive heart failure, myocardial ischemia, heart failure subsequent to myocardial infarction, myocardial infarction, ischemia reperfusion injury, and diseases that arise from thrombotic and prothrombotic states in which the coagulation cascade is activated by administering a therapeutically effective amount of at least one compound of formula I, II, III or IV in a unit dosage form. For such a method, a compound of formula I, II, III or IV can be administered alone or concurrently with a known therapeutic cardiovascular agent, for example, angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, a β-adrenergic receptor antagonist, an antioxidant, or a mixture thereof.

In still another aspect, the invention is directed to a method of treating diabetes mellitus and related diseases, for example, hyperinsulinemia, insulin resistance, obesity, diabetes-induced hypertension, and damage to eyes, kidneys, blood vessels, nerves, autonomic nervous system, skin, connective tissue, or immune system, by administering a therapeutically effective amount of a compound of formula I, II, III or IV in a unit dosage form. For such a method, a compound of formula I, II, III or IV can be administered alone or concurrently with known medicaments suitable for treating diabetes mellitus and related diseases, for example, insulin, hypoglycemic drugs, or a mixture thereof.

DESCRIPTION OF THE INVENTION

The present invention provides for pyridoxine phosphonate analogues such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)alkylphosphonates, and (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)azaalkylphosphonates) and to pyridoxine malonate analogues, such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonates), pharmaceutical compositions, and methods for treatment of cardiovascular and related diseases, and diabetes mellitus and related diseases.

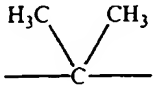
It is to be understood that the recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

It is to be understood that all numbers and fractions thereof are presumed to be modified by the term "about."

It is to be understood that "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds.

It is to be understood that some of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diasteriomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R)- or (S)-. The present invention is meant to imclude all such possible diasteriomers and enantiomers as well as their racemic and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and A geometric isomers. Likewise all tautomeric forms are intended to be included.

The general definitions used herein have the following meanings within the scope of the present invention.

As used herein the term "alkyl" includes a straight or branched saturated aliphatic hydrocarbon redicals, such as, for example, methyl, ethyl, propyl, isopropyl (1-methylethyl),  , butyl, *tert*-butyl (1,1-dimethylethyl), and the like.

As used herein the term "alkoxy" refers to -O-alkyl with alkyl as defined above. Alkoxy groups include those with 1 to 4 carbon atoms in a straight or branched chain, such as, for example, methoxy, ethoxy, propoxy, isopropoxy (1-methylethoxy), butoxy, *tert*-butoxy (1,1-dimethylethoxy), and the like.

As used herein the term "aryl" refers to unsaturated aromatic carbocyclic radicals having a single ring, such as phenyl, or multiple condensed rings, such as naphthyl or anthryl. The term "aryl" also includes substituted aryl comprising aryl substituted on a ring by, for example, C_{1-4} alkyl, C_{1-4} alkoxy, amino, hydroxy, phenyl, nitro, halo, carboxyalkyl or alkanoyloxy. Aryl groups include, for example, phenyl, naphthyl, anthryl, biphenyl, methoxyphenyl, halophenyl, and the like.

As used herein the term "alkylamino" refers to -N-alkyl with alkyl as defined above. Alkylamino groups include those with 1-6 carbons in a straight or branched chain, such as, for example, methylamino, ethylamino, propylamino, and the like.

As used herein the term "arylamino" refers to -N-aryl with aryl as defined above. Arylamino includes -NH-phenyl, -NH-biphenyl, -NH-4-methoxyphenyl, and the like.

As used herein the term "aralkyl" refers to an aryl radical defined as above substituted with an alkyl radical as defined above (e.g. aryl-alkyl-). Aralkyl groups include, for example, phenethyl, benzyl, and naphthylmethyl..

As used herein the term "halo" includes bromo, chloro, and fluoro. Preferably halo is fluoro.

As used herein the term "alkylcarbonyloxy" includes alkyl as defined above bonded to carbonyl bonded to oxygen, such as, for example, acetate, propionate and t-butylcarbonyloxy.

Cardiovascular and related diseases include, for example, hypertension, hypertrophy, congestive heart failure, heart failure subsequent to myocardial

infarction, arrhythmia, myocardial ischemia, myocardial infarction, ischemia reperfusion injury, and diseases that arise from thrombotic and prothrombotic states in which the coagulation cascade is activated.

Heart failure is a pathophysiological condition in which the heart is unable to pump blood at a rate commensurate with the requirement of the metabolizing tissues or can do so only from an elevated filling pressure (increased load). Thus, the heart has a diminished ability to keep up with its workload. Over time, this condition leads to excess fluid accumulation, such as peripheral edema, and is referred to as congestive heart failure.

When an excessive pressure or volume load is imposed on a ventricle, myocardial hypertrophy (i.e., enlargement of the heart muscle) develops as a compensatory mechanism. Hypertrophy permits the ventricle to sustain an increased load because the heart muscle can contract with greater force. However, a ventricle subjected to an abnormally elevated load for a prolonged period eventually fails to sustain an increased load despite the presence of ventricular hypertrophy, and pump failure can ultimately occur.

Heart failure can arise from any disease that affects the heart and interferes with circulation. For example, a disease that increases the heart muscle's workload, such as hypertension, will eventually weaken the force of the heart's contraction. Hypertension is a condition in which there is an increase in resistance to blood flow through the vascular system. This resistance leads to increases in systolic and/or diastolic blood pressures. Hypertension places increased tension on the left ventricular myocardium, causing it to stiffen and hypertrophy, and accelerates the development of atherosclerosis in the coronary arteries. The combination of increased demand and lessened supply increases the likelihood of myocardial ischemia leading to myocardial infarction, sudden death, arrhythmias, and congestive heart failure.

Ischemia is a condition in which an organ or a part of the body fails to receive a sufficient blood supply. When an organ is deprived of a blood supply, it is said to be hypoxic. An organ will become hypoxic even when the blood supply temporarily ceases, such as during a surgical procedure or during temporary artery blockage. Ischemia initially leads to a decrease in or loss of contractile activity.

When the organ affected is the heart, this condition is known as myocardial ischemia, and myocardial ischemia initially leads to abnormal electrical activity. This can generate an arrhythmia. When myocardial ischemia is of sufficient severity and duration, cell injury can progress to cell death—i.e., myocardial infarction—and subsequently to heart failure, hypertrophy, or congestive heart failure.

When blood flow resumes to an organ after temporary cessation, this is known as ischemic reperfusion of the organ. For example, reperfusion of an ischemic myocardium can counter the effects of coronary occlusion, a condition that leads to myocardial ischemia. Ischemic reperfusion to the myocardium can lead to reperfusion arrhythmia or reperfusion injury. The severity of reperfusion injury is affected by numerous factors, such as, for example, duration of ischemia, severity of ischemia, and speed of reperfusion. Conditions observed with ischemia reperfusion injury include neutrophil infiltration, necrosis, and apoptosis.

Drug therapies, using known active ingredients such as vasodilators, angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, diuretics, antithrombolytic agents, α or β-adrenergic receptor antagonists, α-adrenergic receptor antagonists, calcium channel blockers, and the like, are available for treating cardiovascular and related diseases.

Diabetes mellitus and related diseases include hyperinsulinemia, insulin resistance, obesity, diabetes-induced hypertension, and damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, and immune system. Diabetes mellitus is a condition in which blood glucose levels are abnormally high because the body is unable to produce enough insulin to maintain normal blood glucose levels or is unable to adequately respond to the insulin produced. Insulin-dependent diabetes mellitus (often referred to as type I diabetes) arises when the body produces little or no insulin. About 10% of all diabetics have type I diabetes. Noninsulin-dependent diabetes mellitus (often referred to as type II diabetes) arises when the body cannot adequately respond to the insulin that is produced in response to blood glucose levels.

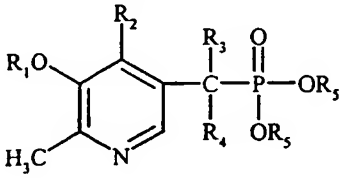
Available treatments include weight control, exercise, diet, and drug therapy. Drug therapy for type I diabetes mellitus requires the administration of insulin; however, drug therapy for type II diabetes mellitus usually involves the

administration of insulin and/or oral hypoglycemic drugs to lower blood glucose levels. If the oral hypoglycemic drugs fail to control blood sugar, then insulin, either alone or concurrently with the hypoglycemic drugs, will usually be administered.

The invention is generally directed to pyridoxine phosphonate analogues such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)alkylphosphonates, (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)azaalkylphosphonates) and to pyridoxine malonate analogues such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonates), compositions including these analogues, and methods of administering pharmaceutical compositions containing a therapeutically effective amount of at least one of these analogues to treat cardiovascular and related diseases or diabetes and related diseases.

To enhance absorption from the digestive tract and across biological membranes, polar groups on a drug molecule can be blocked with lipophilic functions that will be enzymatically cleaved off from the drug after absorption into the circulatory system. Lipophilic moieties can also improve site-specificity and biovailability of the drug. The speed at which the blocking groups are removed can be used to control the rate at which the drug is released. The blocking of polar groups on the drug can also slow first-pass metabolism and excretion. An ester is a common blocking group that is readily hydrolyzed from the drug by endogenous esterases. Bundgaard, *Design and Application of Prodrugs* in *A Textbook of Drug Design and Development* (Krogsgaard-Larson & Bundgaard, eds., Hardwood Academic Publishers, Reading, United Kingdom 1991).

In one embodiment, the compounds of the present invention are analogues of pyridoxal phosphonate. The compounds of the invention include, for example, (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)methylphosphonate analogues. Such compounds are represented by the formula I:



10

I

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3, –CO_2R_6 in which R_6 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2-O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy, alkylcarbonyloxy, alkylamino or arylamino; or

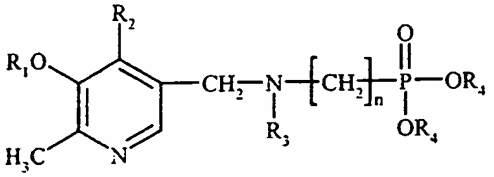
R_3 and R_4 are halo; and

R_5 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_7 in which R_7 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

Examples of compounds of formula I include those where R_1 is hydrogen, or those where R_2 is -CH_2OH, or -CH_2-O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1, or those where R_3 is hydrogen and R_4 is F, MeO- or $CH_3C(O)O$-, or those where R_5 is alkyl or aralkyl. Additional examples of compounds of formula I include those where R_3 and R_4 are F, or those where R_5 is t-butyl or benzyl.

In another aspect, the compounds of the invention include (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)azaalkylphosphonate analogues. Such compounds are represented by formula II:



II

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_5 in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen, alkyl, aryl, or aralkyl;

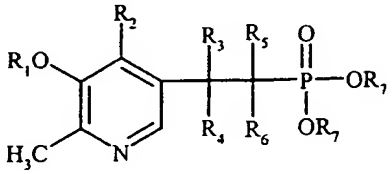
R_4 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_6 in which R_6 is hydrogen, alkyl, aryl, or aralkyl; and

n is 1 to 6;

or a pharmaceutically acceptable acid addition salt thereof.

Examples of compounds of formula II include those where R_1 is hydrogen, or those where R_2 is -CH_2OH, or -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1, or those where R_3 is hydrogen, or those where R_4 is alkyl or hydrogen. Additional examples of compounds of formula II include those where R_4 is ethyl.

In still another aspect, the compounds of the invention include (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)ethylphosphonate analogues. Such compounds are represented by formula III:



III

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_8 in which R_8 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy or alkylcarbonyloxy; or

R_3 and R_4 can be taken together to form =O;

R_5 and R_6 are hydrogen; or

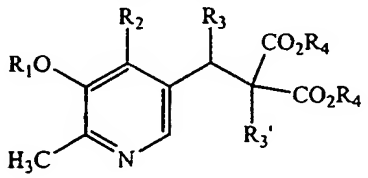
R_5 and R_6 are halo; and

R_7 is hydrogen, alkyl, aryl, aralkyl, or $-CO_2R_8$ in which R_8 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

Examples of compounds of formula III include those where R_1 is hydrogen, or those where R_2 is $-CH_2OH$, or $-CH_2$.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1, or those where R_3 and R_4 taken together form =O, or those where R_5 and R_6 are F, or those where R_7 is alkyl. Additional examples of compounds of formula III include those where R_4 is OH or $CH_3C(O)O-$, those where R_7 is ethyl.

In yet another aspect, the compounds of the invention include pyridoxine malonate analogues such as, for example, ((2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonates). Such compounds are represented by the formula IV:



IV

in which

R_1 is hydrogen or alkyl;

R_2 is $-CHO$, $-CH_2OH$, $-CH_3$ or $-CO_2R_5$ in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is $-CH_2$.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 and R_3' are independently hydrogen or halo; or

R_3 and R_3' taken together constitute a second covalent bond between the carbons to which they are substituent; and

R_4 is hydrogen or alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

Examples of compounds of formula IV include those where R_1 is hydrogen, or those where R_2 is $-CH_2OH$, or $-CH_2$.O-alkyl- in which alkyl is covalently bonded

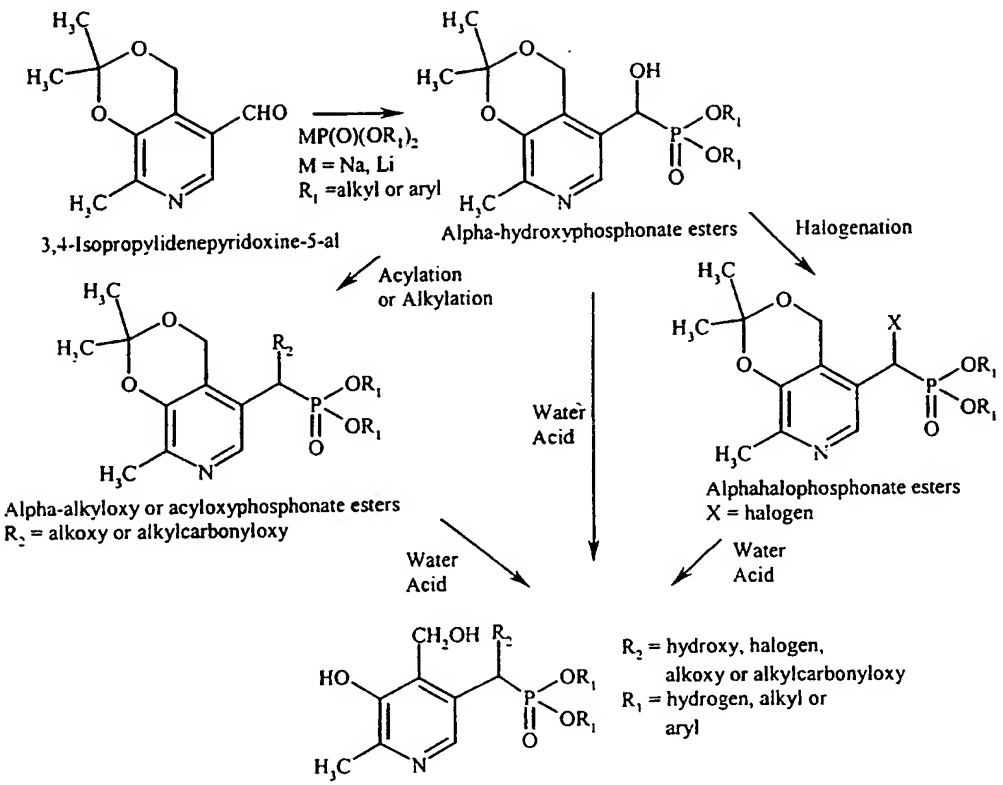
to the oxygen at the 3-position instead of R_1, or those where R_3 and R_3' are independently hydrogen or F, or those where R_4 is hydrogen or ethyl. Additional examples of compounds of formula IV include those where R_3 and R_3' taken together constitute a second covalent bond between the carbons to which they are substituent.

Pharmaceutically acceptable acid addition salts of the compounds of formulas I, II, III or IV include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorus, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glutamine, etc. (see, e.g., Berge et al., *J. Pharmaceutical Science*, 66: 1-19 (1977)).

The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form can be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

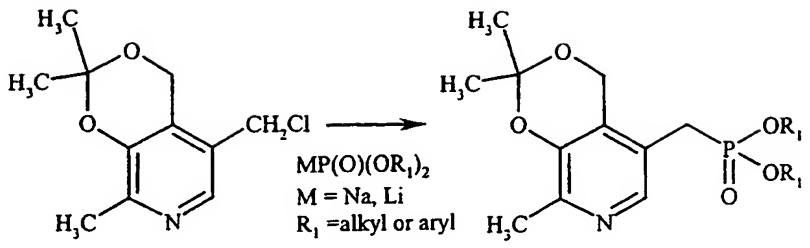
Syntheses

To prepare a compound of formula I, 3,4-isopropylidenepyridoxine-5-al is treated with a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite or dibenzyl phosphite or diphenyl phosphite, to give protected alpha-hydroxyphosphonates. The protected alpha-hydroxyphosphonates can be treated with an acylating agent in an aprotic solvent, such as acetic anhydride in pyridine, or with an alkylating agent, such as methyl iodide and sodium hydride in tetrahydrofuran (THF), to give alpha-alkylcarbonyloxy or alpha-alkyloxyphosphonates esters respectively. Alternatively the protected alpha-hydroxyphosphonates can be treated with an agent to convert the hydroxyl group to a halogen, such as conversion to a fluoro group with DAST (diethylaminosulfurtrifluoride), to prepare the alpha-halophosphonate esters. The isopropylidene protecting group is removed from the fully protected alpha-substituted phosphonates by reacting them with water and an acid, such as 20% water in acetic acid, to prepare the pyridoxine-alpha-substituted phosphonate esters. The ester groups can be removed from the phosphonate groups of the pyridoxine-alpha-substituted phosphonate esters by further treating them with acid in water, such as 20% water in acetic acid, to give the corresponding phosphonic acids as can be seen in the following scheme.



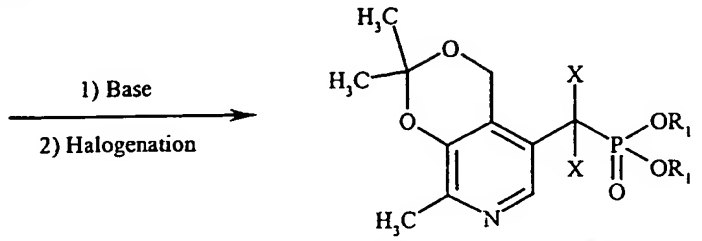
Pyridoxine-alpha-substituted phosphonate esters and acids

Alternatively, to prepare a compound of formula I, 3,4-isopropylidenepyridoxine-5-halide is treated with a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite or dibenzyl phosphite or diphenyl phosphite, to give protected phosphonates. The protected phosphonates are treated with a base, such as sodium hexamethyldisilazane (NaHMDS), and a halogenating agent, such as N-fluorobenzenesulfonimide (NFSi), to provide the dihalophosphonates as can be seen in the following scheme.



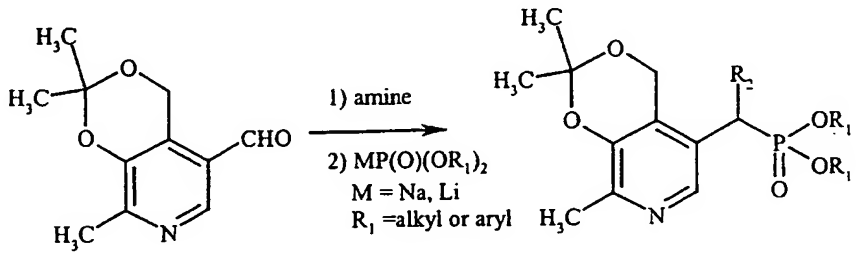
3,4-Isopropylidenepyridoxine-5-chloride

Phosphonate esters



Dihalophosphonate esters
X = halogen

Alternatively, to prepare a compound of formula I, 3,4-isopropylidenepyridoxine-5-al is treated with an amine, such as p-methoxyaniline or p-aminobiphenyl, and a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite, dibenzyl phosphite or diphenyl phosphite, to give protected aminophosphonates as can be seen in the following scheme.

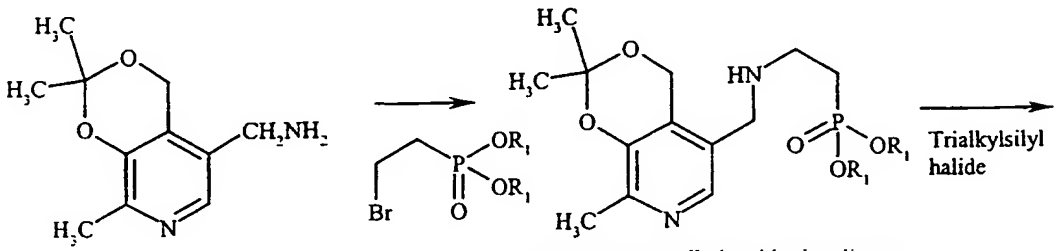


3,4-Isopropylidenepyridoxine-5-al

Aminophosphonates
R1 = alkyl or aryl
R_2 = N-alkyl or N-aryl

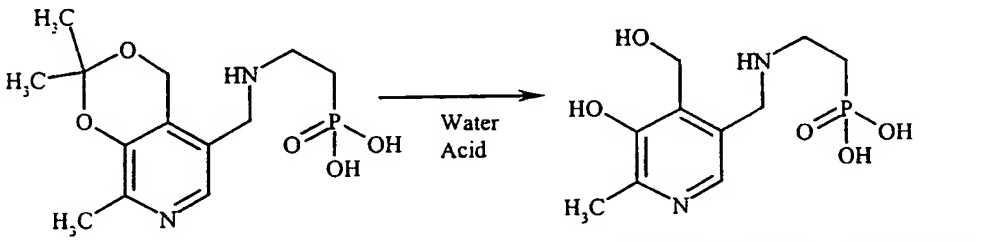
To prepare a compound of formula II, 3,4-isopropylidenepyridoxine-5-amine is used as a starting material. The amine is treated with a haloalkylphosphonate diester, such as diethyl bromomethylphosphonate, to give 5'-phosphonoazaalkylpyridine diesters. Reaction of the 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diesters with a trialkylsilyl halide, such as trimethylsilyl bromide, in an aprotic solvent, such as acetonitrile, removes the ester

groups of the phosphonate diester to provide the corresponding free 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diacid. The acetonide protecting group on the 3 and 4 position of the pyridoxine ring on the 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diacid can be removed by reaction with acid and water, such as 20% water in acetic acid as can be seen in the following scheme.



3,4-Isopropylidene pyridoxine-5-amine

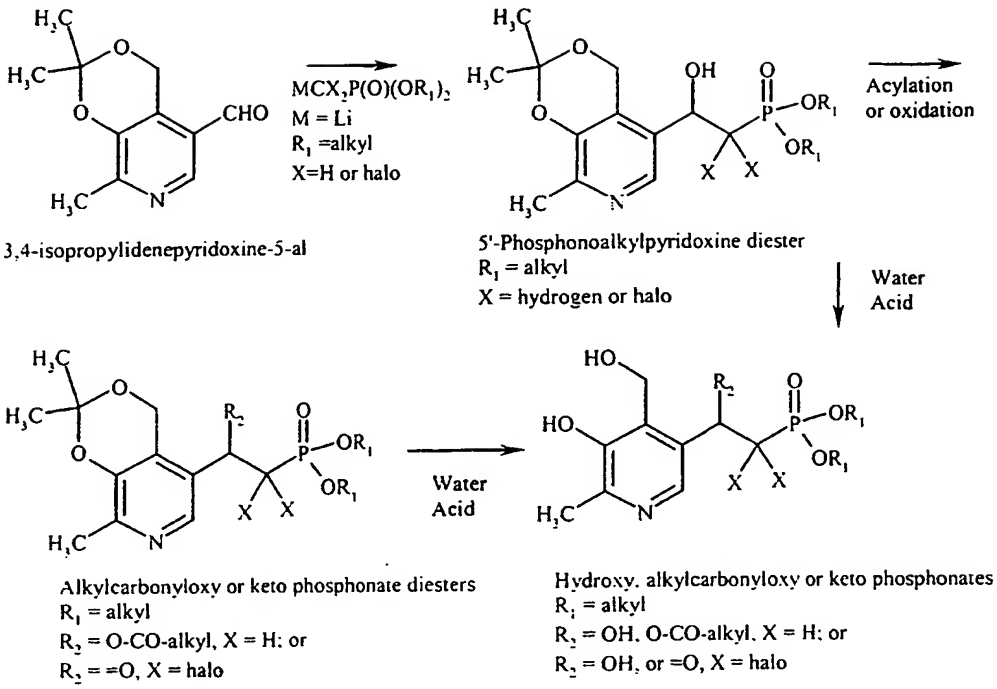
5'-Phosphonoazaalkylpyridoxine diesters
R_1 = alkyl



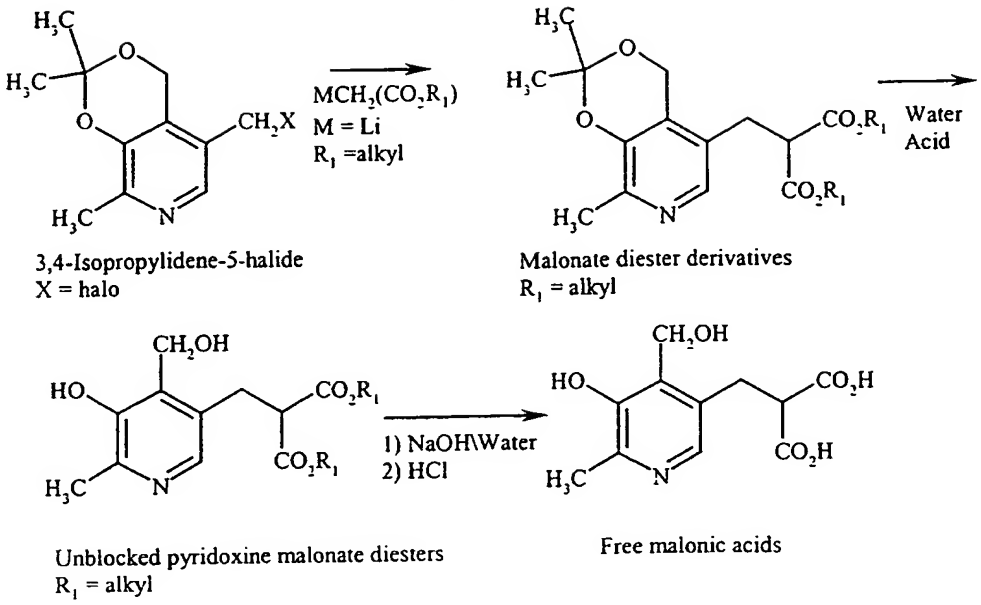
3,4-Isopropylidene 5-phosphonoazaalkylpyridoxine diacid

5-Phosphonoazaalkylpyridoxine diacid

To prepare a compound of formula III, 3,4-isopropylidenepyridoxine-5-al is reacted with a metal salt of a methyl, or dihalomethyl, phosphonate diester to produce 5'-phosphonoalkylpyridoxine diesters. The 5'-hydroxyl group of this product is acylated by an acylating agent, such as acetic anhydride in pyridine, to provide the corresponding O-acyl derivatives respectively, or oxidized to the keto functional group by an oxidizing agent, such as manganese dioxide. The blocking group at the 3 and 4 positions and the phosphonate ester groups of the hydroxy, alkylcarbonyloxy and keto phosphonate diesters are hydrolysed by reaction with acid and water, such as 20% water in acetic acid, to provide the corresponding phosphonate diesters, without the blocking group at the 3 and 4 position. These reactions are illustrated in the following scheme.



To prepare a compound of formula IV, the 3,4-isopropylidenepyridoxine-5-halide is reacted with a metal salt of a malonate diester to give the malonate diester derivative. The malonate diester derivative is hydrolysed in aqueous acid, such as 20% water in acetic acid, to remove the blocking group at the 3 and 4 position of the pyridoxine ring. The ester groups of the malonate are hydrolysed with water and base, such as sodium hydroxide in water, followed by acidification to provide the corresponding free malonic acid products. These reactions are illustrated in the following scheme.



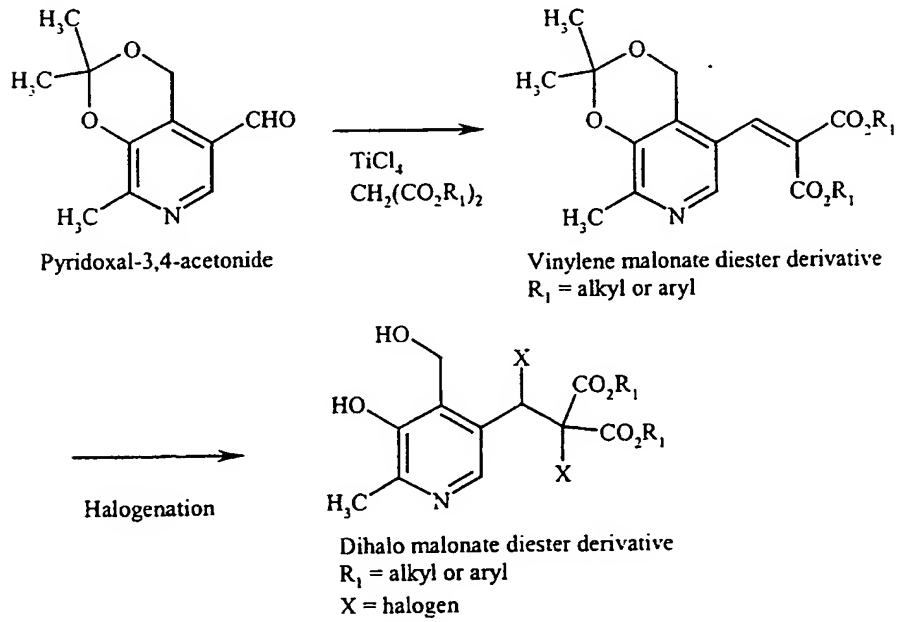
3,4-Isopropylidene-5-halide
X = halo

Malonate diester derivatives
R_1 = alkyl

Unblocked pyridoxine malonate diesters
R_1 = alkyl

Free malonic acids

Alternatively, to prepare a compound of formula IV, 3,4-isopropylidenepyridoxine-5-al is reacted with a condensing agent, such as titanium tetrachloride, and a malonate diester, such as diethyl malonate, to provide a vinylene malonate diester. The vinylene malonate diester is reacted with a fluorinating agent, such as Selectfluor, to give a dihalomalonate derivative. These reactions are illustrated in the following scheme.



Pyridoxal-3,4-acetonide

Vinylene malonate diester derivative
R_1 = alkyl or aryl

Dihalo malonate diester derivative
R_1 = alkyl or aryl
X = halogen

One skilled in the art would recognize variations in the sequence of steps and would recognize variations in the appropriate reaction conditions from the analogous reactions shown or otherwise known that can be appropriately used in the above-described processes to make the compounds of formula I, II, III or IV herein.

The products of the reactions described herein are isolated by conventional means such as extraction, distillation, chromatography, and the like.

Methods of Use

In accordance with the present invention, the analogues can be used in the treatment of cardiovascular and related diseases; and in the treatment of diabetes mellitus and related diseases.

Cardiovascular and related diseases include, for example, hypertension, hypertrophy, congestive heart failure, heart failure subsequent to myocardial infarction, arrhythmia, myocardial ischemia, myocardial infarction, ischemia reperfusion injury, and diseases that arise from thrombotic and prothrombotic states in which the coagulation cascade is activated.

Diabetes mellitus and related diseases include, for example, hyperinsulinemia, insulin resistance, obesity, diabetes-induced hypertension, and damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, and immune system.

"Treatment" and "treating" as used herein include preventing, inhibiting, alleviating, and healing cardiovascular and related diseases; diabetes mellitus and related diseases; or symptoms thereof. Treatment can be carried out by administering a therapeutically effective amount of a compound of the invention. A "therapeutically effective amount" as used herein includes a prophylactic amount, for example, an amount effective for preventing or protecting against cardiovascular and related diseases; diabetes mellitus and related diseases; or symptoms thereof, and amounts effective for alleviating or healing cardiovascular and related diseases; or diabetes mellitus and related diseases; or symptoms thereof.

A physician or veterinarian of ordinary skill readily determines a subject who is exhibiting symptoms of any one or more of the diseases described above. Regardless of the route of administration selected, the compounds of the present

invention of formula I, II, III or IV or a pharmaceutically acceptable acid addition salt thereof can be formulated into pharmaceutically acceptable unit dosage forms by conventional methods known to the pharmaceutical art. An effective but nontoxic quantity of the compound is employed in treatment. The compounds can be administered in enteral unit dosage forms, such as, for example, tablets, sustained-release tablets, enteric coated tablets, capsules, sustained-release capsules, enteric coated capsules, pills, powders, granules, solutions, and the like. They can also be administered parenterally, such as, for example, subcutaneously, intramuscularly, intradermally, intramammarally, intravenously, and other administrative methods known in the art.

Although it is possible for a compound of the invention to be administered alone in a unit dosage form, preferably the compound is administered in admixture as a pharmaceutical composition. A pharmaceutical composition comprises a pharmaceutically acceptable carrier and at least one compound of formula I, II, III or IV, or a pharmaceutically acceptable acid addition salt thereof. A pharmaceutically acceptable carrier includes, but is not limited to, physiological saline, ringers, phosphate-buffered saline, and other carriers known in the art. Pharmaceutical compositions can also include additives, for example, stabilizers, antioxidants, colorants, excipients, binders, thickeners, dispersing agents, readsorpotion enhancers, buffers, surfactants, preservatives, emulsifiers, isotonizing agents, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

Methods of preparing pharmaceutical compositions containing a pharmaceutically acceptable carrier and at least one compound of formula I, II, III or IV or a pharmaceutically acceptable acid addition salt thereof are known to those of skill in the art. All methods can include the step of bringing the compound of the invention in association with the carrier and additives. The formulations generally are prepared by uniformly and intimately bringing the compound of the invention into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired unit dosage form.

The ordinarily skilled physician or veterinarian will readily determine and prescribe the therapeutically effective amount of the compound to treat the disease for which treatment is administered. In so proceeding, the physician or veterinarian could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained. Typically, the particular disease, the severity of the disease, the compound to be administered, the route of administration, and the characteristics of the mammal to be treated, for example, age, sex, and weight, are considered in determining the effective amount to administer. Administering a therapeutic amount of a compound of the invention for treating cardiovascular and related diseases; diabetes mellitus and related diseases; or symptoms thereof, is in a range of 0.1-100 mg/kg of a patient's body weight, more preferably in the range of 0.5-50 mg/kg of a patient's body weight, per daily dose. The compound can be administered for periods of short and long duration. Although some individual situations can warrant to the contrary, short-term administration, for example, 30 days or less, of doses larger than 25 mg/kg of a patient's body weight is preferred to long-term administration. When long-term administration, for example, months or years, is required, the suggested dose should not exceed 25 mg/kg of a patient's body weight.

A therapeutically effective amount of a compound for treating the above-identified diseases or symptoms thereof can be administered prior to, concurrently with, or after the onset of the disease or symptom.

The compound also can be administered to treat cardiovascular and related diseases, for example, hypertrophy, hypertension, congestive heart failure, heart failure subsequent to myocardial infarction, myocardial ischemia, ischemia reperfusion injury, arrhythmia, or myocardial infarction. Preferably, the cardiovascular disease treated is hypertrophy or congestive heart failure. Still preferably, the cardiovascular disease treated is arrhythmia. Also preferably, the cardiovascular disease treated is ischemia reperfusion injury.

The compound can also be administered to treat cardiovascular diseases and other diseases that arise from thrombotic and prothrombotic states in which the coagulation cascade is activated, such as, for example, deep vein thrombosis, disseminated intravascular coagulopathy, Kasabach-Merritt syndrome, pulmonary

embolism, myocardial infarction, stroke, thromboembolic complications of surgery, and peripheral arterial occlusion. A compound of the invention may also be useful in the treatment of adult respiratory distress syndrome, septic shock, septicemia, or inflammatory responses, such as edema and acute or chronic atherosclerosis, because thrombin has been shown to activate a large number of cells outside of the coagulation process, such as, for example, neutrophils, fibroblasts, endothelial cells, and smooth muscle cells.

Moreover, the compound can be administered concurrently with compounds that are already known to be suitable for treating the above-identified diseases. For example, methods of the invention include concurrently administering at least one compound of formula I, II, III or IV a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof with a therapeutic cardiovascular compound to treat hypertrophy, hypertension, congestive heart failure, heart failure subsequent to myocardial infarction, myocardial ischemia, ischemia reperfusion injury, arrhythmia, or myocardial infarction. Preferably the cardiovascular disease treated is hypertrophy or congestive heart failure. Still preferably, the cardiovascular disease treated is arrhythmia. Also preferably, the cardiovascular disease treated is ischemia reperfusion injury.

Therapeutic cardiovascular compounds that can be concurrently administered with at least one compound of the invention include an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, an antioxidant, and a mixture thereof. A compound of the invention also can be concurrently administered with PPADS (pyridoxal phosphate-6-azophenyl-2',4'-disulphonic acid), also a therapeutic cardiovascular compound, or with PPADS and another known therapeutic cardiovascular compound as already described.

Preferably a therapeutic cardiovascular compound, which is concurrently administered with at least one compound of formula I, II, III or IV, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof, is an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, or a diuretic. Still preferably, the therapeutic cardiovascular compound is an α-adrenergic

receptor antagonist. Also preferably, the therapeutic cardiovascular compound is a calcium channel blocker.

These therapeutic cardiovascular compounds are generally used to treat cardiovascular and related diseases as well as symptoms thereof. A skilled physician or veterinarian readily determines a subject who is exhibiting symptoms of any one or more of the diseases described above and makes the determination about which compound is generally suitable for treating specific cardiovascular conditions and symptoms.

For example, myocardial ischemia can be treated by the administration of, for example, angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, or a mixture thereof. In some instances, congestive heart failure can be treated by the administration of, for example, angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, or a mixture thereof.

Myocardial infarction can be treated by the administration of, for example, angiotensin converting enzyme inhibitor, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, or a mixture thereof.

Hypertension can be treated by the administration of, for example, angiotensin converting enzyme inhibitor, a calcium channel blocker, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, or a mixture thereof.

Moreover, arrhythmia can be treated by the administration of, for example, a calcium channel blocker, a β-adrenergic receptor antagonist, or a mixture thereof.

Antithrombolytic agents are used for reducing or removing blood clots from arteries.

Hypertrophy can be treated by the administration of, for example, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, or a mixture thereof.

Ischemia reperfusion injury can be treated by the administration of, for example, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, or a mixture thereof.

Known angiotensin converting enzyme inhibitors include, for example, captopril, enalapril, lisinopril, benazapril, fosinopril, quinapril, ramipril, spirapril, imidapril, and moexipril.

Examples of known angiotensin II receptor antagonists include both angiotensin I receptor subtype antagonists and angiotensin II receptor subtype antagonists. Suitable antiotensin II receptor antagonists include losartan and valsartan.

Suitable calcium channel blockers include, for example, verapamil, diltiazem, nicardipine, nifedipine, amlodipine, felodipine, nimodipine, and bepridil.

Antithrombolytic agents known in the art include antiplatelet agents, aspirin, and heparin.

Examples of known β-adrenergic receptor antagonists include atenolol, propranolol, timolol, and metoprolol.

Suitable vasodilators include, for example, hydralazine, nitroglycerin, and isosorbide dinitrate.

Suitable diuretics include, for example, furosemide, diuril, amiloride, and hydrodiuril.

Suitable α-adrenergic receptor antagonists include, for example, prazosin, doxazocin, and labetalol.

Suitable antioxidants include vitamin E, vitamin C, and isoflavones.

At least one compound of formula I, II, III or IV, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof and a therapeutic cardiovascular compound can be administered concurrently. "Concurrent administration" and "concurrently administering" as used herein includes administering a compound of the invention and a therapeutic cardiovascular compound in admixture, such as, for example, in a pharmaceutical composition or in solution, or as separate compounds, such as, for example, separate pharmaceutical compositions or solutions administered consecutively, simultaneously, or at different times but not so distant in time such that the compound of the invention and the

therapeutic cardiovascular compound cannot interact and a lower dosage amount of the active ingredient cannot be administered.

At least one compound of formula I, II, III or IV, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof also can be administered to treat diabetes mellitus and related diseases. Preferably the disease treated is type I diabetes, type II diabetes, or obesity. Also preferably, the disease treated is damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system. Still preferably, the disease treated is insulin resistance or hyperinsulinemia. And preferably, the disease treated is diabetes-induced hypertension.

The method of the invention also includes concurrently administering at least one compound of formula I, II, III or IV, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof with insulin and/or a hypoglycemic compound to treat diabetes mellitus and related diseases. The compound can be administered concurrently with insulin and/or a hypoglycemic compound to treat type I diabetes, type II diabetes, or obesity. Preferably the compound can be administered concurrently with insulin and/or hypoglycemic compound to treat damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system. Still preferably, the compound can be administered concurrently with insulin and/or hypoglycemic compound to treat insulin resistance or hyperinsulinemia. Also preferably, the compound can be administered concurrently with insulin and/or hypoglycemic compound to treat diabetes-induced hypertension.

A compound typically can be administered concurrently with insulin to treat type I diabetes, type II diabetes, and related conditions and symptoms. For type II diabetes, insulin resistance, hyperinsulinemia, diabetes-induced hypertension, obesity, or damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system, a compound can be administered concurrently with a hypoglycemic compound instead of insulin. Alternatively, a compound can be administered concurrently with insulin and a hypoglycemic compound to treat type II diabetes, insulin resistance, hyperinsulinemia, diabetes-induced hypertension, obesity, or damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system.

"Concurrent administration" and "concurrently administering" as used herein includes administering at least one compound of formula I, II, III or IV, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof and insulin and/or a hypoglycemic compound in admixture, such as, for example, in a pharmaceutical composition, or as separate compounds, such as, for example, separate pharmaceutical compositions administered consecutively, simultaneously, or at different times. Preferably, if the compound and insulin and/or hypoglycemic compound are administered separately, they are not administered so distant in time from each other that the compound and the insulin and/or hypoglycemic compound cannot interact and a lower dosage amount of insulin and/or hypoglycemic compound cannot be administered.

Suitable hypoglycemic compounds include, for example, metformin, acarbose, acetohexamide, glimepiride, tolazamide, glipizide, glyburide, tolbutamide, chlorpropamide, and a mixture thereof. Preferably the hypoglycemic compound is tolbutamide.

This invention will be further characterized by the following examples. These examples are not meant to limit the scope of the invention, which has been fully set forth in the foregoing description. Variations within the scope of the invention will be apparent to those skilled in the art.

EXAMPLES

All reagents used in the following Examples can be purchased from Aldrich Chemical Company (Milwaukee, WI or Allentown, PA).

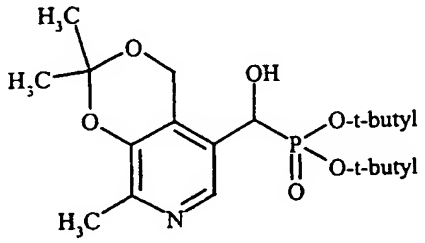
Example 1: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethylphosphonate

Di-tert-butyl phosphite (16.3 g, 84 mmol) was added to a solution of NaH (3.49 g, 60%, 87.2 mmol) in THF (60 mL) under nitrogen at 0°C. The temperature of the resulting solution was raised to room temperature and the solution stirred for 15 min, then cooled to 0°C again. To this solution, (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (11.41 g, 55.05 mmol) in THF (30 mL) was slowly added then the temperature raised to room temperature again and stirring continued for 2 h. The reaction was quenched by adding saturated $NaHCO_3$ (40 ml), and diluted with diethyl ether (200 mL). The ether layer was separated, washed with saturated aqueous $NaHCO_3$ (40 ml, 5%), then saturated brine (3 x 20 mL). The ether layer was dried ($MgSO_4$), filtered and evaporated to give crude product as a colorless solid. This solid was washed with hexane to remove the oil (from the NaH) and unreacted phosphite. The solid was recrystallized from a mixture of diethyl ether : hexane : ethyl acetate (230 mL : 70 mL : 15 mL). The colorless crystal (17.9 g, 81%) were filtered and washed with hexane.

^{1}H NMR ($CDCl_3$): 1.42 (9H, d), 1.46 (9H, d), 1.51 (6H, d), 2.38 (3H, s), 4.70 (1H, d), 4.89-5.13 (2H, m), 8.11 (1H, s).

^{31}P NMR (H-decoupled, $CDCl_3$): 13.43 (s).

This structure can be represented by formula V:



V

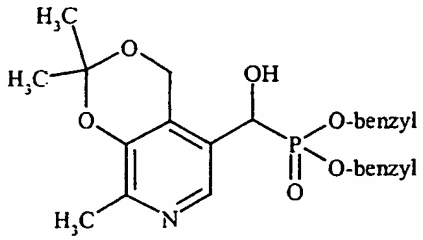
PAGE INTENTIONALLY LEFT BLANK

Example 2: Synthesis of dibenzyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethylphosphonate

Dibenzyl phosphite (1.89 g, 9.62 mmol) was mixed with the (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (1.00g, 4.81mmol) and stirred at room temperature for an hour. To this thick syrup was added activated basic alumina (1g). The reaction mixture was then stirred at 80°C for one hour. The reaction mixture was diluted with dichloromethane (50 mL), and filtered through Celite to remove alumina. The dichloromethane solution was washed with saturated, aqueous $NaHCO_3$ (20 mL), then saturated brine (3 x 10 mL). The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to give crude product as a colorless solid. The crude product was purified by silica gel column chromatography, using ether: hexanes (1:2) as eluent to give 1.3 g (58%).

^1H NMR ($CDCl_3$): 1.30 (3H, s), 1.45 (3H, s), 2.30 (3H, s), 4.86-4.99 (7H, s), 7.18-8.07 (10H, s), 8.08 (1H, s).

This structure can be represented by formula VI:



VI

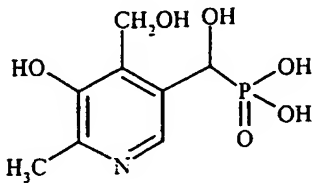
Example 3: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethyl phosphonic Acid

The product of Example 1 above, of formula V, (10 g, 24.9 mmol) was dissolved in acetic acid (80% in water, 100 ml) and heated at 60°C for 1 d. Colorless precipitate was formed, however, the reaction was not complete. Another 50 ml of 80% acetic acid in water was added to the mixture and the mixture stirred at 60°C for another day. The solid was filtered off, washed with cold water, then methanol and dried to give a colorless solid (4.78 g, 77%).

^{1}H NMR (D_2O): 2.47 (3H, s), 4.75-4.79 (2H, m), 5.15-5.19 (1H, d), 7.82 (1H, s).

^{31}P NMR (H-decoupled D_2O): 14.87 (s).

This structure can be represented by formula VII:



VII

Example 4: Synthesis of dibenzyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethylphosphonate

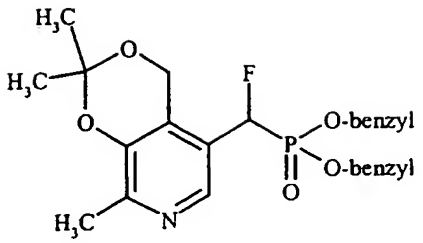
The protected alpha-hydroxy phosphonate from Example 2 above of structure VI (1.0 g, 2.49 mmol) was dissolved in dichloromethane (10 mL), and the solution cooled to -78°C. To this solution was added diethylaminosulfurtrifluoride (DAST) (0.8 g, 4.98 mmol). The reaction was stirred at -78°C under nitrogen for 20 minutes then allowed to stand at room temperature overnight. The reaction mixture was diluted with dichloromethane (50 ml), and washed with saturated, aqueous $NaHCO_3$ (125 mL). The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to give crude fluorophosphonate as a yellow solid. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (2:1) as the eluent to give 600 mg (60%).

^{1}H NMR ($CDCl_3$): 1.42 (3H, s), 1.52 (3H, s), 2.40 (3H, s), 4.91-4.97 (6H, m), 5.46-5.61 (1H, dd), 7.23- 7.34 (10H, m), 8.01 (1H, s).

^{31}P NMR (H-decoupled, F-coupled, $CDCl_3$): 16.36-16.08 (d).

This structure can be represented by formula VIII:

32



VIII

Example 5: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethylphosphonate

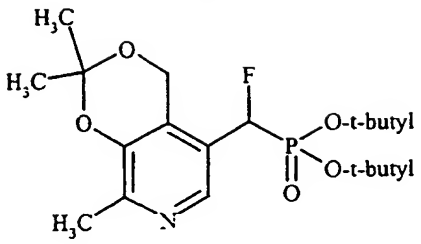
The protected alpha-hydroxy phosphonate from Example 1 of structure V (3 g, 7.55 mmol) was dissolved in dichloromethane (30 mL), and the solution cooled to -78°C. To this solution was added diethylaminosulfurtrifluoride (DAST) (1.22 g, 7.57 mmol). The reaction was stirred at -78°C under nitrogen for 5 minutes, quenched by addition of saturated, aqueous $NaHCO_3$ (2 mL) then allowed to warm room temperature. The reaction mixture was diluted with dichloromethane (50 ml), and washed with saturated, aqueous $NaHCO_3$ (2 x 20 mL). The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to give crude fluorophosphonate. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (1:1) as the eluent to give 350 mg (12%).

^1H NMR ($CDCl_3$): 1.44 (9H, s), 1.46 (9H, s), 1.52 (3H, s), 1.56 (3H,s), 2.41 (3H, s), 4.98-5.14 (2H, m), 5.32-5.52 (1H, dd), 8.03 (1H, s).

^{31}P NMR (H-decoupled, F-coupled, $CDCl_3$): 6.53, 7.24.

^{19}F NMR (H-decoupled, $CDCl_3$): -202.6, -203.0

This structure can be represented by formula IX:



IX

Example 6: Synthesis of di-t-butyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethyl phosphonate

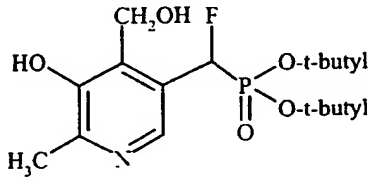
The protected di-t-butyl alpha-fluoro phosphonate from Example 5 of structure IX (3.2 g 7.8 mmol) was dissolved in acetic acid (80% in water, 50 ml) and heated at 60°C for 24 hours. The pale yellow solid was filtered off, washed with cold water and methanol, and then dried to give a creamy solid (2.21 g, 70%).

^{1}H NMR ($CDCl_3$): 1.41 (9H, s), 1.44 (9H, s), 1.49 (3H, s), 1.51 (3H, s), 2.42 (3H, s), 4.99-5.07 (2H, m), 5.33-5.51 (1H, d,d), 8.04 (1H, s).

^{31}P NMR (H-decoupled, F-Coupled, $CDCl_3$): 7.10-7.80 (d).

^{19}F NMR (H, P-Coupled, $CDCl_3$): -203.07 to -202.61 (dd).

This structure can be represented by formula X:



X

Example 7: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethyl phosphonic acid

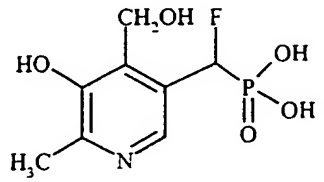
The protected di-t-butyl alpha-fluoro phosphonate from Example 5 of structure IX (200 mg, 0.5 mmol) was dissolved in acetic acid (80% in water, 15 ml) and heated at 75°C for 24 hours. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product (183 mg) was purified by column chromatography on silica using chloroform:methanol:water (65:35:2) as eluent to give 60 mg (55%).

^{1}H NMR (D_2O): 2.46 (3H, bs), 4.65-4.90 (2H, dd), 5.81-6.01 (1H, dd), 7.74 (1H, bs).

^{31}P NMR (H-decoupled, F-Coupled, $CDCl_3$): 9.3 (d).

^{19}F NMR (H, P-Coupled, $CDCl_3$): -197 to –196 (dd).

This structure can be represented by formula XI:



XI

Example 8: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)acetoxymethylphosphonate

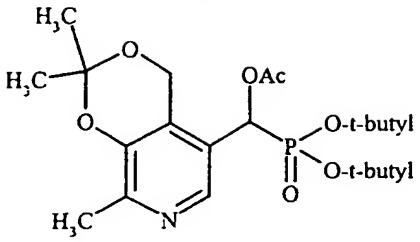
The product of Example 1 above, of formula V (1.0 g, 2.49 mmol) was dissolved in dichloromethane (20 mL), the solution cooled to -5°C, and pyridine (2 mL) added, followed by acetic anhydride (1mL). The reaction temperature was slowly allowed to reach room temperature. After one hour, the reaction was quenched by adding dilute aqueous hydrochloric acid (10%, 75 mL), and then diluted with dichloromethane (25 mL). Afterm separation of the aqueous layer the methylene chloride layer washed with saturated $NaHCO_3$ (2 x 20 mL). The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to give crude alpha acetoxy phosphonate as a colorless solid. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (2:1) as the eluent to give the product in good yield.

^1H NMR ($CDCl_3$): 1.31 (9H, d), 1.36 (9H, d), 1.49 (6H, d), 2.1 (3H s), 2.38 (3H, s), 5.04 (2H, d), 5.72-5.76 (1H, d), 8.11 (1H, s).

^{31}P NMR (H-decoupled, $CDCl_3$): 13.43 (s).

This structure can be represented by formula XII:

35



XII

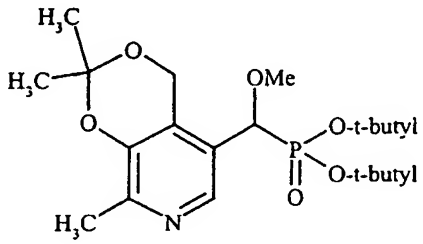
Example 9: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methoxymethylphosphonate

The product of Example 1 above, of formula V (300 mg, 0.75 mmol) was dissolved in 15ml of THF and reaction vessel was purged with N_2 gas. Sodium hydride (21 mg, 0.9 mmol) was added, and the solution stirred for 5 minutes before cooling to 0°C. Methyl iodide (160 mg, 1.1 mmol) was then injected and reaction vessel was gradually allowed to reach room temperature. TLC (ethyl acetate) indicated that the reaction was complete in 3 hours. The soution was diluted with methylene chloride (250 mL), washed with dilute, aqueous HCL (10%, 100 mL), then saturated, aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel using ethyl acetate/hexanes (1:1) as the eluent to give 132 mg (32%).

^{1}H NMR ($CDCl_3$): 1.41 (18H, s), 1.51 (3H, s), 1.54 (3H, s), 2.40 (3H, s), 3.33 (3H, s), 4.20-4.26 (1H, d), 5.05 (2H, bs), 8.01 (1H, s).

^{31}P NMR (H-decoupled, $CDCl_3$): 10.88 (s).

This structure can be represented by formula XIII:



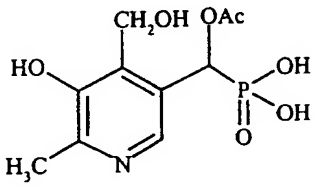
XIII

Example 10: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)acetoxymethyl phosphonic Acid

The product of Example 8 above, of formula XII, (50 mg, 0.11 mmol) was added to acetic acid (80% in water) and stirred for 24 hours at 60°C. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product was purified by chromatography on silica gel column using CH_2Cl_2/MeOH/H_2O (65:35:4) as eluent to give 22.8 mg (76%).

^{1}H NMR (D_2O): 2.23 (3H, s); 2.51 (3H, s), 4.6 – 5.1 (2H, m), 6.1 (1H, d), 7.85 (1H, s).

This structure can be represented by formula XIV:



XIV

Example 11: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methoxymethyl phosphonic Acid

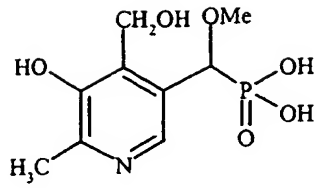
The product of Example 9 above, of formula XIII (132 mg, 0.32 mmol) was dissolved in acetic acid (80% in water, 25mL) and stirred at 60°C for 24 hours. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product was purified by chromatography on silica gel column using CH_2Cl_2/MeOH/H_2O (65:35:4) as eluent to give the product in good yield.

^{1}H NMR (D_2O): 2.52 (3H, s), 3.32 (3H, s), 4.47-4.88 (2H, m), 7.87 (1H, s).

^{31}P NMR (H-decoupled, D_2O): 13.31 (s)

This structure can be represented by formula XV:

37



XV

Example 12: Synthesis of dibenzyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)difluoromethylphosphonate

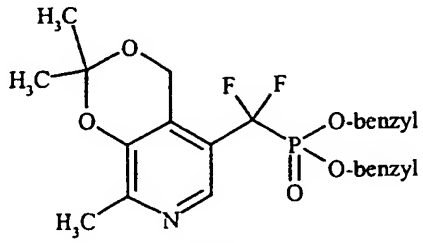
To a solution of dibenzyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylphosphonate (115 mg, 0.253 mmol) in THF (10 mL) was added NaHMDS (1 M, 0.56 mL, 0.56 mmol). The reaction mixture was cooled to-78°C. After 15 minutes, NFSi (237 mg, 0.75 mmol) was added to the reaction mixture. The temperature of the reaction mixture was slowly warmed to -20°C. The solution was diluted with Et_2O, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica using ethyl acetate:hexanes (2:1) as eluent to give the dibenzyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)difluoromethylphosphonate in good yields.

^{1}H NMR ($CDCl_3$) 1.53 (s, 6H), 2.45 (d, 3H), 5.34 (d, 2H), 7.09-7.39 (m, 14H), 8.29 (s,1H).

^{31}P NMR ($CDCl_3$) -2.15 (t)

^{19}F NMR ($CDCl_3$) -105.7 (d)

This structure can be represented by formula XVI:



XVI

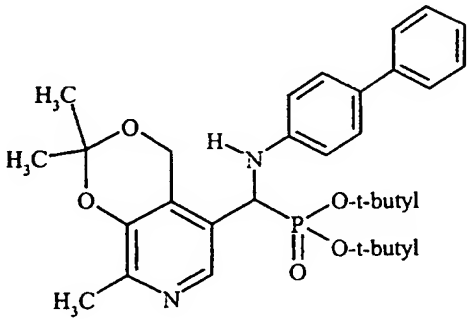
Example 13: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-biphenylamino)methylphosphonate

The (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (424 mg, 2.19 mmol) and 4-aminobiphenyl (360 mg, 2.12 mmol) was refluxed in benzene (20 mL) under nitrogen, using a Dean-Stark trap to remove water, for 15 hours. The crude reaction mixture was evaporated, dissolved in THF (20 mL) and added to a flask containing di-t-butyl phosphite (955 mg, 5.12 mmol) in THF (20 mL) and NaH (270 mg, 57% in oil, 6.41 mmol) and stirred at 0°C for two hours. The solution was diluted with Et_2O, washed with saturated, aqueous $NaHCO_3$ (40 mL), brine (20 mL), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel using hexane:diethyl ether (2:1) to give di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-biphenylamino)methylphosphonate in modest yields.

^{1}H NMR ($CDCl_3$) 8.40 (1H, d,), 7.50-7.41 (2H, m), 7.40-7.30 (4H, m), 7.28-7.10 (1H, m), 6.54 (1H, d), 5.24 (1H, dd,), 5.07 (1H, dd,), 4.65 (1H, dd,), 4.44 (1H, dd,), 2.40 (3H, d), 1.58 (3H, s), 1.49 (3H, s), 1.43 (9H, s), 1.41 (9H, s).

^{31}P NMR (H-decoupled, $CDCl_3$): 13.1 (s).

This structure can be represented by formula XVII:



XVII

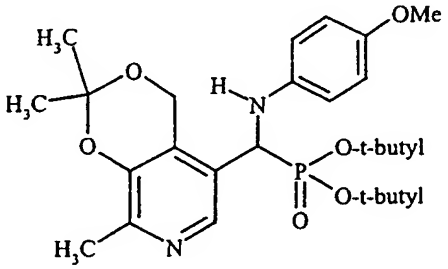
Example 14: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-methoxyphenylamino)methylphosphonate

(α^4,3-O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (2.5 g, 12.1 mmol) and 4-aminoanisole (1.41 g, 11.4 mmol) was refluxed in benzene (100 mL) under nitrogen, using a Dean-Stark trap to remove water, for 15 hours. The reaction mixture was evaporated to give 3.02 g of crude imine. The crude imine (370 mg, 1.19 mmol) was dissolved in THF (20 mL) and added to a flask containing di-t-butyl phosphite (955 mg, 5.1 mmol) in THF (20 mL) and NaH (208 mg, 57% in oil, 4.94 mmol) and stirred at 0°C for two hours and at room temperature for 24 hours. The solution was diluted with Et_2O, washed with saturated, aqueous $NaHCO_3$ (40 mL), brine (40 mL), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel using hexane:diethyl ether (2:1) to give di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-methoxyphenylamino)methylphosphonate in modest yields.

^{1}H NMR ($CDCl_3$) 8.09 (1H, d), 6.70-6.60 (2H, m), 6.47-6.36 (2H, m), 5.18 (1H, dd), 4.98 (1H, dd), 4.36-4.20 (2H, m), 3.65 (3H, s), 2.35 (3H, s), 1.54 (3H, s), 1.45 (3H, s), 1.39 (9H, s), 1.38 (9H, s).

^{31}P NMR (decoupled, $CDCl_3$): δ 13.5 ppm.

This structure can be represented by formula XVIII:



XVIII

Example 15: Synthesis of di-t-butyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonate

(α^4,3-O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylbromide (Imperalli *et al*, J. Org. Chem., 60, 1891-1894 (1995)) (

1.08 g. 4.0 mmol) in anhydrous DMF (20 ml) was treated with sodium azide (260 mg, 4.0 mmol) at room temperature. After one hour stirring at room temperature, the solution was extracted with diethyl ether (5 x 20 mL). The combined extracts were washed with water (10 mL) , and brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by chromatography on silica gel using ethyl ether: hexanes (2:1) as eluent to give the azide as a colorless liquid (552mg, 60%).

^{1}H NMR (CDCl3, TMS) 1.57 (s, 6H), 2.42 (s, 3H), 4.23 (s, 2H), 4.86 (s, 2H), 7.96 (s, 1H).

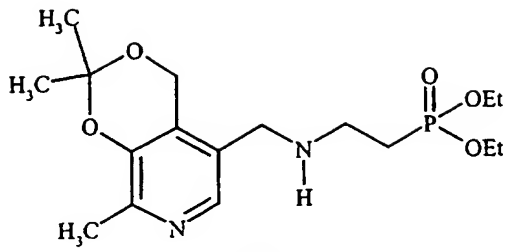
The purified azide (100 mg, 0.4 mmol) was dissolved in 95% ethanol and hydrogenated at 1 atm in presence of Lindlar catalyst (50 mg) for one hour. The catalyst was removed by filtration (Celite), and the solvent removed to give the crude amine. Purification by chromatography on silica gel using CH_2Cl_2:MeOH (5:1) as eluent gave the product (80 mg, 82%) 1HNMR (CD_2Cl_2) 1.53 (s, 6H), 2.34 (s, 3H), 3.72 (s, 2H), 4.91 (s, 2H), 5.31 (s, 2H), 7.93 (s, 1H).

The (α^4,3-O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylamine, from above, (416 mg, 2 mmol) was heated in saturated, aqueous sodium bicarbonate solution (10 mL) to 95°C, followed by slow addition of diethyl 2-bromoethylphosphonate (0.09 mL, 0.5mmol) and the reaction stirred at 95° C overnight. The solution is evaporated using toluene to codistill the water. The crude product is triturated with ethyl acetate to dissolve the crude organic product. Chromatography on silica gel using methylene chloride:methanol:hexanes (5:1:5) gave 76 mg (41%).

^{1}Hnmr ($CDCl_3$, TMS) 1.27 (t, 6H), 1.51 (s, 6H), 1.91 (t, 2H), 2.35 (s, 3H), 2.85 (t, 2H), 3.62 (s, 2H), 4.03 (m, 4H), 4.91 (s, 2H), 7.88 (s, 1H).

^{31}P NMR (H-decoupled, $CDCl_3$): 31.00 (s)

This structure can be represented by formula XIX:



XIX

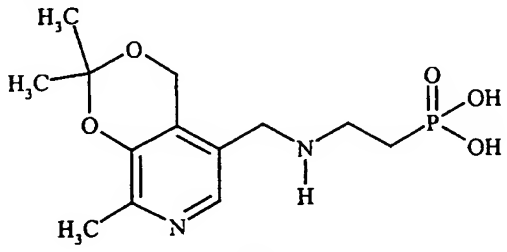
Example 16: Synthesis of (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonic acid

The product of Example 15, of formula XIX (280 mg, 0.75 mmol) was stirred in a mixture of acetonitile (6 mL) and trimethylsilylbromide (TMSBr) (574 mg, 3.75 mmol) overnight at room temperature. The solvent was evaporated and the crude product was purified by chromatography on silica gel using dichloromethane:methanol:water (65:35:6) giving 188 mg (91%).

^{1}H NMR (D_2O) 1.65 (s, 6H), 2.02 (m,2H), 2.42 (s,3H), 3.40 (m, 2H), 4.24 (s, 2H), 5.12 (s, 2H), 8.11 (s, 1H).

^{31}P NMR (H-decoupled, D_2O): 18.90 (s).

This structure can be represented by formula XX:



XX

Example 17: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonic acid

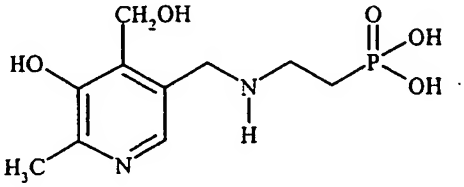
The product of Example 16, of formula XX (168 mg, 0.53 mmol) was dissolved in acetic acid (80% in water, 10 mL) and heated to 60°C for 5 hours. The solvent was removed by evaporation using toluene to codistill the water. The crude

product was purified by chromatography on C-18 reverse phase silica gel using methanol:water (4:1) as eluent to give 57 mg (39%).

^{1}H NMR (D_2O) 2.05 (m, 2H), 2.52 (s, 3H), 3.38 (m, 2H), 4.42 (s, 2H), 4.96 (s, 2H), 7.87(s, 1H).

^{31}P NMR (H-decoupled, D_2O): 18.90 (s).

This structure can be represented by formula XXI:



XXI

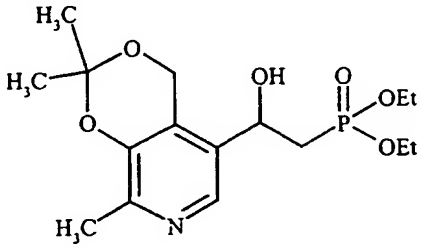
Example 18: Synthesis of diethyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxyethylphosphonate

To a solution of diethyl methyl phosphite (0.29 mL, 2 mmol) in THF (20mL) was added BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol), followed by (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (414 mg, 2 mmol) and the reaction mixture stirred at -78°C for two hours. The solution was evaporated, dissolved in dichloromethane (50 mL), washed with saturated, aqueous $NaHCO_3$, dried ($MgSO_4$), evaporated and purified by chromatography on silica gel using ethyl acetate:hexane (1:2) as eluent to give 625 mg (87%).

^{1}H NMR($CDCl_3$, TMS) 1.33 (m, 6H), 1.54 (s, 6H), 2.20 (m, 2H), 2.38 (s, 3H), 4.12 (m, 4H), 4.94 (s, 2H), 4.94 (s, 2H), 5.04 (t, 1H), 8.02 (s, 1H).

^{31}P NMR (H-decoupled, $CDCl_3$): 29.03 (s).

This structure can be represented by formula XXII:



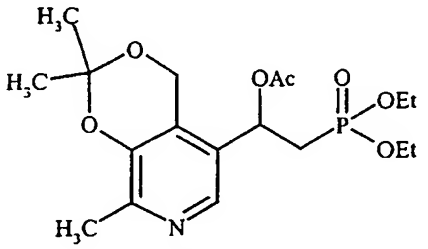
Example 19: Synthesis of diethyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2acetoxyethylphosphonate

The product of Example 18, of structure XXII (300 mg, 0.84 mmol) was acetylated in pyridine (0.5 mL) and acetic anhydride (0.25 mL) at 0°C for 5 minutes followed by 3 hours at room temperature. The solvent was removed by evaporation using toluene to codistill the solvents and the crude product was dissolved in dichloromethane (10 mL). This was washed with dilute HCl (10%, 5 mL), then saturated, aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Chromatography on silica gel using ethyl acetate:hexane (1:1) gave 258 mg (71%).

^1H NMR($CDCl_3$, TMS) 1.21 (m, 6H), 1.54 (s, 6H), 2.03 (s,3H), 3.97 (m , 4H), 5.07 (dd, 2H), 5.83 (dd, 1H), 8.02 (s, 1H).

^{31}P NMR (H-decoupled, $CDCl_3$): 25.01 (s).

This structure can be represented by formula XXIII:



XXIII

Example 20: Synthesis of diethyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxy-1,1-difluoroethylphosphonate

To a solution of lithiumdiisopropylamide (LDA) (2.0 M, 1 mL, 2 mmol) in THF (5 mL) was added BuLi (0.5 M, 0.2 mL, 0.1mmol). The mixture was cooled to -40°C followed by the addition of diethyl difluoromethyl phosphonate (0.32 mL, 2 mmol) and the reaction mixture stirred at this temperature for 30 minutes. The solution was cooled to -78°C and (α^4,3-O-Isopropylidene-3-hydroxy-4-

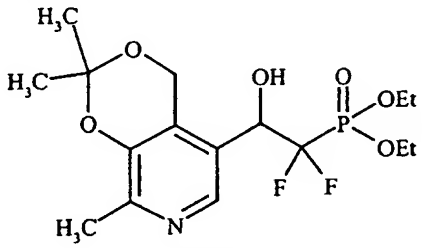
hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (414 mg, 2 mmol) added in THF (2 mL). The solution was allowed to come to room temperature and stirred overnight. The solvent was evaporated, the residue dissolved in dichloromethane (20 mL), washed with saturated, aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Purification by chromatography on silica gel using ethyl acetate:hexane (2:1) gave 528 mg (67%)

^1H NMR ($CDCl_3$, TMS) 1.35 (t, 3H), 1.38 (t, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.39 (s,3H), 4.29 (m, 4H), 4.96 (dd , 3H), 8.09 (s, 1H).

^{19}F NMR ($CDCl_3$) -125.99 (ddd), -114.55 (ddd)

^{31}P NMR (H-decoupled, $CDCl_3$): 7.22 (dd).

This structure can be represented by formula XXIV:



XXIV

Example 21: Synthesis of diethyl (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-oxo-1,1-difluoroethylphosphonate

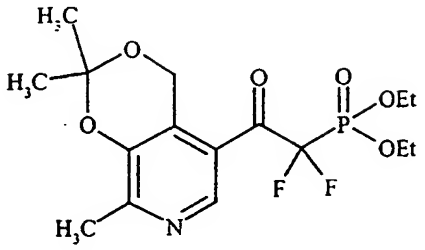
The product of Example 20, of structure XXIV, (420 mg, 1.06 mmol) was dissolved in toluene (50 mL) and MnO_2 (651 mg, 636 mmol) added. The mixture was heated to 50°C and stirred overnight. The solution was cooled, filtered (Celite) and the solvent evaporated to give the crude product. Purification by chromatography on silica gel ethyl acetate (1:2) gave 201 mg (48%).

^1H nmr ($CDCl_3$, TMS) 1.39 (q, 6H), 1.56 (d, 6H), 2.51 (s,3H), 4.34 (m, 4H), 5.08 (s, 2H), 8.88 (s, 1H).

^{19}F NMR ($CDCl_3$) -109.86 (d).

^{31}P NMR (H-decoupled, $CDCl_3$): 3.96 (t)

This structure can be represented by formula XXV:



XXV

Example 22: Synthesis of diethyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxy-1,1-difluoroethylphosphonate

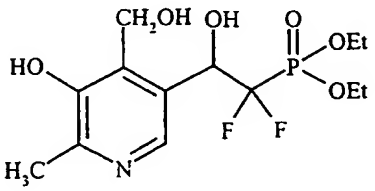
The product of Example 20, of structure XXIV (489 mg, 1.26 mmol) was dissolved in acetic acid (80% in water, 20 mL) and heated at 80°C for 6 hours. The solvent was removed by evaporation by codistilling with toluene to remove last traces of acetic acid. The crude product was purified by chromatography on silica gel using dichloromethane:methanol:hexane (5:1:5) as eluent to give 171 mg (38%).

^{1}H NMR (CD_3OD) 1.32 (t, 3H), 1.37 (t, 3H), 2.43 (s,3H), 4.30 (m , 4H), 4.93 (dd, 2H), 5.39 (m, 2H), 8.07 (s, 1H).

^{19}F NMR (CD_3OD) -125.55 (dd), -115.77 (dd).

^{31}P NMR (H-decoupled, MeOD): 7.82 (dd).

This structure can be represented by formula XXVI:



XXVI

Example 23: Synthesis of diethyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-oxo-1,1-difluoroethylphosphonate

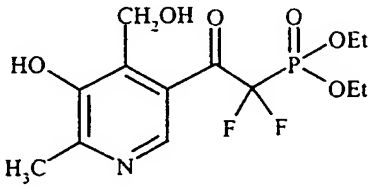
The product of Example 21, of structure XXV (198 mg, 0.51 mmol) was dissolved in acetic acid (80% in water, 20 mL) and heated at 80°C for 6 hours. The solvent was removed by evaporation by codistilling with toluene to remove last traces of acetic acid. The crude product was purified by chromatography on silica gel using dichloromethane:methanol:hexane (5:1:5) as eluent to give 25 mg (14%).

^{1}H NMR ($CDCl_3$, TMS) 1.38 (m, 6H), 2.37 (s,3H), 4.33 (m, 4H), 4.92 (s, 1H), 7.88 (s, 1H).

^{19}F ($CDCl_3$) -118.32 (d)

^{31}P NMR (H-decoupled, $CDCl_3$): 5.90 (t)

This structure can be represented by formula XXVII:



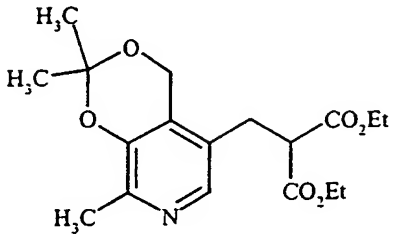
XXVII

Example 24: Synthesis of diethyl (α^4,3-O-isopropylidene-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonate

To a solution of diethyl malonate (0.76 mL, 798 mg, 4.98 mmol) in tetrahydrofuran (THF) (5 mL) was added LDA (5 M, 1 mL, 5.0 mmol) and stirred at 0°C for 5 minutes. (α^4,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylbromide (Imperalli *et al*, J. Org. Chem., 60, 1891-1894 (1995)) (1.36 g, 5.0 mmol) in THF (5 mL) was added. The reaction was stirred for 2 hours at 0°C. The solvent was evaporated and the residue was dissolved in Et_2O. This was washed with water, dried ($MgSO_4$) and evaporated to give the crude product. Purification of the crude mixture by chromatography on silica gel column using diethyl ether:hexane (1:1) gave the malonate derivative 769 mg (44%).

^{1}H NMR ($CDCl_3$, TMS) 1.23 (t, 6H), 1.54 (s, 6H), 2.37 (s, 3H), 3.04 (d, 2H), 3.63 (t, 1H), 4.18 (q, 4H), 4.86 (s, 2H), 7.87 (s, 1H).

This structure can be represented by formula XXVIII:



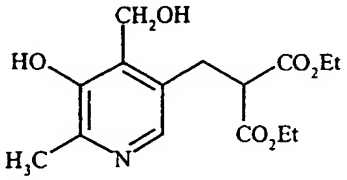
XXVIII

Example 25: Synthesis of diethyl (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonate

The product of Example 24, of structure XXVIII (769 mg, 2.18 mmol) was dissolved in acetic acid (80% in water, 25 mL) and heated at 80°C for 3 hours. The solvent was removed by evaporation using toluene to codistill the solvents. The crude product was purified by chromatography on silica gel using ethyl acetate:hexane (4:1) as eluent to give 620 mg (91%).

^{1}H NMR (MeOD) δ 1.19 (t, 6H), 2.38 (s, 3H), 3.18 (d, J=7.6, 2H), 3.74 (t, J=7.7, 1H), 4.14 (q, 4H), 4.87 (s, 2H), 7.70 (s, 1H).

This structure can be represented by formula XXIX:



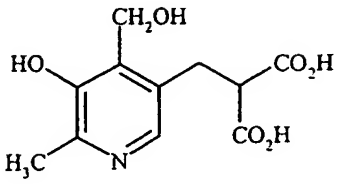
XXIX

Example 26: Synthesis of (2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonic acid

The product of Example 25, of structure XXIX (620 mg, 2.0 mmol) was dissolved in aqueous NaOH (2 M, 4 mL) and stirred at room temperature for 1 hour. The reaction was quenched by adding 6 N HCl to give pH 4 to 5. The solution was diluted with 95% ethanol, separated from the precipitated salts and evaporated to give 540 mg.

^{1}H NMR (DMSO) 2.58 (s, 3H), 3.24 (d, 2H), 3.81 (t, 1H), 4.78 (s, 2H), 8.05 (s, 1H).

This structure can be represented by formula XXX:



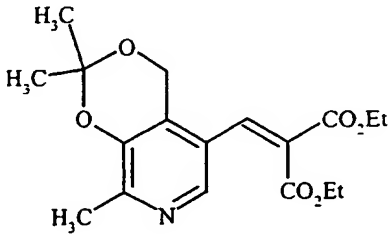
XXX

Example 27: Synthesis of diethyl (α^4,3-O-Isopropylidene-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethylene)malonate

(α^4,3-O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (1.035 g, 5.5mmol) was dissolved in benzene (10 mL) and, diethyl malonate (0.8 mL, 5 mmol), piperidine (0.08 mL) and acetic acid (0.09 mL) added. The solution was heated at 80°C for 4 hours. The solution was diluted with diethyl ether (50 mL) and washed with dilute HCl, aqueous, saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by chromatography on silica gel using diethyl ether:hexane (1:2) as eluent to give 1.4 g (80%).

^{1}H NMR ($CDCl_3$) 1.24 (t, 3H), 1.33 (t, 3H), 1.55 (s, 6H), 2.42 (s, 3H), 4.27 (q, 2H), 4.31 (q, 2H), 4.83 (s, 2H), 7.52 (s, 1H), 8.06 (s, 1H).

This structure can be represented by formula XXXI:



XXXI

Example 28: Synthesis of diethyl 2-(α^4,3-O-Isopropylidene-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl)-1,2-difluoro-1,1-dicarbethoxyethane

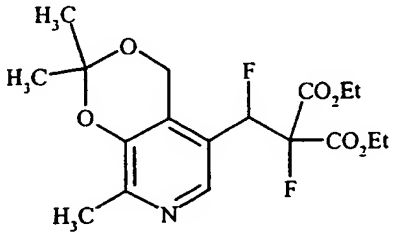
The product of Example 27, of structure XXXI ((354mg, 1 mmol) was dissolved in acetonitrile (10 mL) and Pyr/HF (1 mL) added, followed by 1-

(choromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor reagent) (359 mg, 1mmol). The reaction mixture was stirred at room temperature for 4 hours. The solution was diluted with diethyl ether (60 mL) and washed with water, $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated. Purification by chromatography on silica gel using diethyl ether:hexane (2:1) as eluent gave 90 mg (29%).

^1H NMR ($CDCl_3$, TMS) 1.21 (t, 3H), 1.26 (t,3H), 2.48 (s, 3H), 3.7(d, 1H) ,4.14-4.21(m, 4H), 5.01-5.03 (m, 2H), 5.03(d,1H), 7.85 (s, 1H),

^{19}F NMR ($CDCl_3$) -181.33, -181.44.

This structure can be represented by formula XXXII:



XXXII

Example 29: In Vivo Assay – Coronary Artery Ligation

Myocardial infarction was produced in male Sprague-Dawley rats (300-400 g) by occlusion of the left coronary artery. The rats were housed in clear cages in a temperature (19-22°C) and humidity (50-55% RH) controlled room on a 12 hour light-dark cycle. Food and water were supplied *ad libitum*. Rats were anaesthized with 1-5% isoflurane in 100% O_2 (2L/minute flow rate). The skin was incised along the left sternal border and the 4th rib was cut proximal to the sternum and a retractor was inserted. The pericardial sac was opened and the heart externalized. The left anterior descending coronary artery was ligated approximately 2mm from its origin on the aorta using a 6-0 silk suture. The heart was then repositioned in the chest and the incision closed via purse-string sutures. Sham-operated rats underwent identical treatment except that the artery was not ligated. Mortality due to surgery was less

than 1%. All animals were allowed to recover, receiving food and water ad libitum for 21 days. Hemodynamic and histological assessments were made.

Occlusion of the coronary artery in rats has been shown to produce myocardial cell damage, which results in scar formation in the left ventricle and heart dysfunction. While the complete healing of the scar occurs within 3 weeks of the coronary occlusion, mild, moderate and severe stages of congestive heart failure have been reported to occur at 4, 8 and 16 weeks after ligation. Accordingly, the contractile dysfunction seen at 3 weeks after coronary occlusion in rats is due to acute ischemic changes.

Rats were divided at random into five groups: sham operated, coronary artery ligated (untreated), coronary artery ligated (pyridoxal-5'-phosphate (P5P) treatment), coronary artery ligated (compound VII treated) and coronary artery ligated (compound XI treated). Treatment with P5P, compound VII and compound XI began 1 hour after coronary occlusion (or sham operation), and continued for 21 days. P5P, compound VII or compound XI (10 mg/kg) were administered daily (9AM) by gastric tube. This dosage was chosen based on previous experience with P5P.

Mortality in all groups occurred only within the first 24h after coronary ligation. While in the untreated group 50% of the rats died, the mortality rate dropped to 17-25% in the treated groups (Table I).

Table I - Mortality

Example 30 - In Vivo – Hemodynamic Changes

The animals prepared as described in Example 29 were anaesthetized with an injected cocktail of ketamine hydrochloirde (60 mg/kg) and xylazine (10 mg/kg). To maintain adequate ventilation, the trachea was intubated. The right carotid artery was exposed and a microtip pressure transducer was introduced (Model SPR-249, Millar, Houston, TX) into the left ventricle. The catheter was secured with a silk ligature around the artery, and various hemodynamic parameters including left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP), rate of contraction (+dP/dt), and rate of relaxation (-dP/dt), were recorded and calculated with Acknowledge 3.1 software (Biopac Systems Inc.). The animals were allowed 5-10 minutes to stabilize, after which parameters were measured as averages over three readings.

Average +dP/dt and –dP/dt values were significantly reduced in the untreated group compared to the sham control group. The experimental groups receiving P5P, compound VII or compound XI all experienced statistically significant recoveries in +dP/dt (rate of contraction) and –dP/dt (rate of relaxation) values (Table II).

LVSP (left ventricular systolic pressure) was significantly decreased in the untreated group compared to the sham control group, after 21 days of coronary ligation. There was a statistically significant recovery in LVSP in the group receiving compound compound VII, but not in the other treatment groups. Average LVEDP was significantly increased in the untreated group, compared to the sham control group. Treatment with P5P, compound VII or compound XI yielded similar significantly reduced rises in LVEDP in response to coronary occlusion. These results are tabulated below; data are expressed as mean±SD (Table II).

Table II – Hemodynamic Parameters

Sham	9	133.0±9.3	5.7±1.3	10899.6±462.4	11231.9±896.7	
Untreated	10	112.9±11.9#	21.1±4.0#	8011.8±735.8 #	8404.4±775.8 #	
P5P	10	120.0±10.6	12.6±3.7 *	9417.4±853.0 *	9854.9±861.2 *	
VII	10	124.9±10.8 *	13.7±5.3 *	9731.7±915.3 *	10174.4±900.8 *	
XI	9	115.0±12.1	16.2±5.2 *	9182.9±717.0 *	9670.9±755 *	
LVSP	LVEDP	-dP/dt	+dP/dT			

* P<0.05 significantly different from Untreated group (t-test)

# P<0.05 significantly different from Sham Control group (t-test)

Example 31 - In Vivo – Hypertrophy

Hypertrophy is a physiological condition of enlargement (increased mass) due to increased stress. Cardiac hypertrophy is assessed by calculating the heart to body mass ratio. As seen in Table III, treatment with P5P, compound VII or compound XI results in a significant decrease in cardiac hypertrophy, in the rat model described in Example 29.

Table III – Cardiac Hypertophy

	Heart Weight/Body Weight
Sham	0.0027± 0.0001
Untreated	0.0035 ± 0.0002 #
P5P	0.0032 ± 0.0001 *
MC-5723	0.0031 ± 0.0004 *
MC-5422	0.0032 ± 0.0002 *

* P<0.05 significantly different from Untreated
# P<0.05 significantly different from Sham Control

Example 32 - In Vivo – Infarct Size and Scar Mass

After 21 days, once the hemodynamic data were obtained, the animals were sacrificed and both average dry scar mass to left ventricle mass (n=5/group) and infarct size (n=5/group) were measured. For infarct size measurement, hearts from the untreated and P5P/compound VII/compound XI-treated groups were fixed in 10% formalin and embedded in. Six evenly spaced slices were cut across the left ventricle. 5 μM sections were cut from each slice and mounted. Sections were stained with Trichrome to discriminate between fibrous scar and noninfarcted tissue. Using the free-drawing line tool in Scion Image v4.02b, infarct internal perimeter and left ventricle internal perimeter lengths were traced *per oculum* for each section. Significant transmural scars were taken into account. Infarct size was then expressed as the average scar perimeter/ventricle perimeter ratio. Scar mass measurements were obtained by drying excised scar tissue and left ventricles at 50-60°C for 72hrs.

The P5P-treated group had a significantly reduced dry scar to left ventricle mass ratio. The compound XI-treated group had scar/ventricle ratio reductions similar in magnitude to that seen in the P5P group. The compound VII-treated group, however, experienced a far more dramatic reduction in scar size than the other groups, with some animals not even having visible scars. This drastic reduction was also reflected in the infarct size measurements. In the untreated control group, average infarct size (as a percentage of left ventricle size) was about 45%; in the P5P and compound XI groups, the infarct size was reduced to about 20%. In the compound VII group, however, infarct size was reduced to lower than 10% (Table IV).

Table IV – Infarct size and scar mass

	Scar Wt./LV Wt.	Infarct Size (%LV)
Sham	0	0
Untreated	0.269±0.026	45.4±2.3
P5P	0.090±0.026 *	21.0±4.6 *
VII	0.013±0.030 *	7.2±1.4 *
XI	0.090±0.019 *	21.5±3.0 *

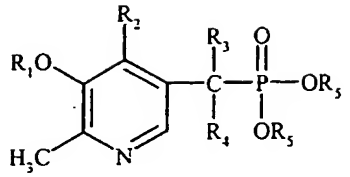
* $P<0.05$ significantly different from Untreated

Although embodiments of the invention have been described above, it is not limited thereto, and it will be apparent to persons skilled in the art that numerous modifications and variations form part of the present invention insofar as they do not depart from the spirit, nature, and scope of the claimed and described invention.

All publications, patents, and patent documents described herein are incorporated by reference as if fully set forth.

WE CLAIM:

1. A compound of the formula I



I

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3, –CO_2R_6 in which R_6 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy, alkylcarbonyloxy, alkylamino or arylamino; or

R_3 and R_4 are halo; and

R_5 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_7 in which R_7 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, wherein R_1 is hydrogen.

3. A compound according to claim 1, wherein R_2 is -CH_2OH, or -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1.

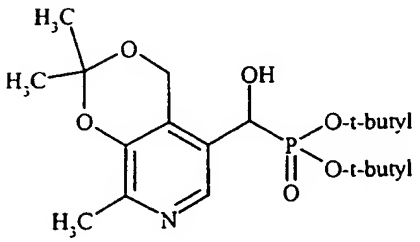
4. A compound according to claim 1, wherein R_3 is hydrogen and R_4 is F, MeO-, or $CH_3C(O)O$-.

5. A compound according to claim 1, wherein R_3 and R_4 are F.

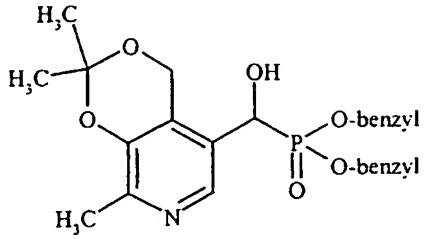
6. A compound according to claim 1, wherein R_5 is alkyl or aralkyl.

7. A compound according to claim 6, wherein R_5 is t-butyl or benzyl.

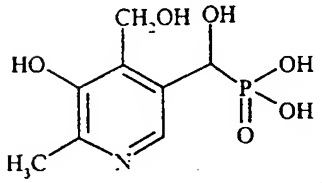
8. A compound according to claim 1 selected from



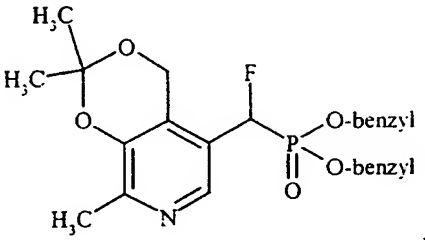
,



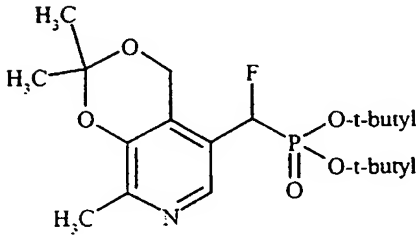
,



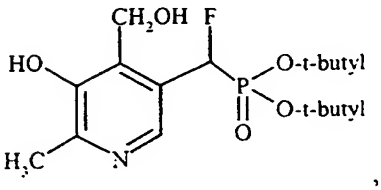
,



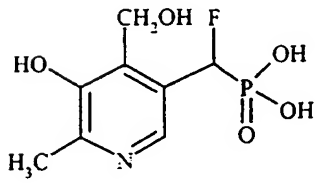
,



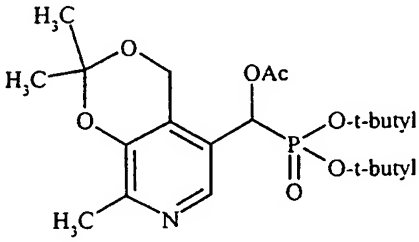
,



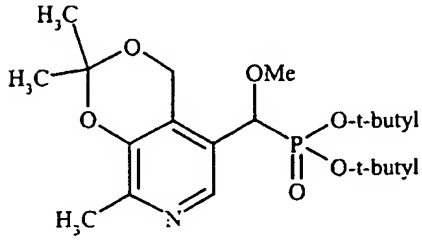
,



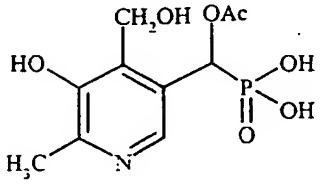
,



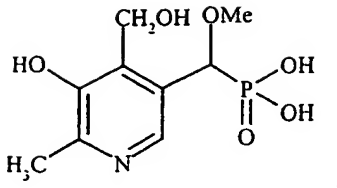
,



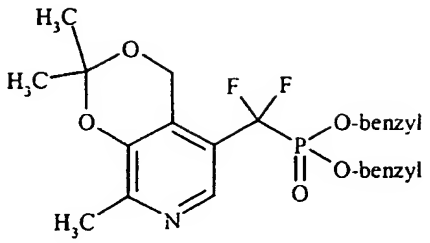
,



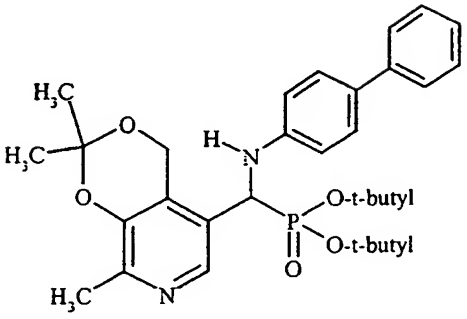
,



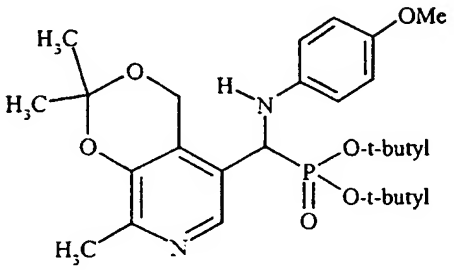
,



,



, and



.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to claim 1.

10. A pharmaceutical composition of claim 9, wherein the pharmaceutical composition is in a form suitable for enteral or parenteral administration.

11. A method of treating hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

12. The method of claim 11, wherein the compound is administered enterally or parenterally.

13. The method of claim 11, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

14. A method of treating myocardial infarction in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

15. The method of claim 14, wherein the compound is administered enterally or parenterally.

16. The method of claim 14, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, an antithromblytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

17. A method of treating ischemia reperfusion injury in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

18. The method of claim 17, wherein the compound is administered enterally or parenterally.

19. The method of claim 17, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

20. A method of treating myocardial ischemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

21. The method of claim 20, wherein the compound is administered enterally or parenterally.

22. The method of claim 20, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

23. A method of treating congestive heart failure in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

24. The method of claim 23, wherein the compound is administered enterally or parenterally.

25. The method of claim 23, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, and a mixture thereof.

26. A method of treating arrhythmia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

27. The method of claim 26, wherein the compound is administered enterally or parenterally.

28. The method of claim 26, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of a calcium channel blocker, a β-adrenergic receptor antagonist, and a mixture thereof.

29. A method of reducing blood clots in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

30. The method of claim 29, wherein the compound is administered enterally or parenterally.

31. The method of claim 29, wherein the compound is administered concurrently with an antithrombolytic agent.

32. A method of treating hypertrophy in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

33. The method of claim 32, wherein the compound is administered enterally or parenterally.

34. The method of claim 32, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

35. A method of treating a disease that arises from thrombotic and prothrombotic states in which the coagulation cascade is activated in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

36. The method of claim 35, wherein the compound is administered enterally or parenterally.

37. The method of claim 35, wherein the disease comprises deep vein thrombosis.

38. The method of claim 35, wherein the disease comprises disseminated intravascular coagulopathy.

39. The method of claim 35, wherein the disease comprises pulmonary embolism.

40. A method of treating diabetes mellitus in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

41. The method according to claim 40, wherein the diabetes mellitus treated is insulin-dependent diabetes mellitus.

42. The method according to claim 41, wherein the compound is administered concurrently with insulin.

43. The method according to claim 40, wherein the diabetes mellitus treated is noninsulin-dependent diabetes mellitus.

44. The method according to claim 42, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

45. The method according to claim 40, wherein the compound is administered enterally or parenterally.

46. A method of treating insulin resistance in a mammal comprising concurrently administering to the mammal a therapeutically effective amount of a cmpound according to claim 1 in a unit dosage form.

47. The method of claim 46, wherein the compound is administered enterally or parenterally.

48. The method of claim 46, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

49. A method of treating hyperinsulinemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

50. The method of claim 49, wherein the compound is administered enterally or parenterally.

51. The method of claim 49, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

52. A method of treating diabetes-induced hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

53. The method of claim 52, wherein the compound is administered enterally or parenterally.

54. The method of claim 52, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

55. A method of treating diabetes-related damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

56. The method of claim 55, wherein the compound is administered enterally or parenterally.

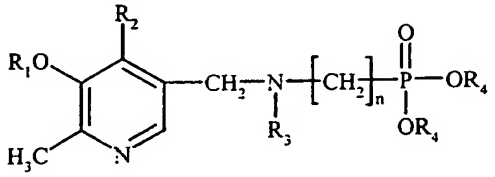
57. The method of claim 55, wherein the compound is administered concurrently with
insulin or a hypoglycemic compound.

58. A method of treating obesity in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 1 in a unit dosage form.

59. The method of claim 58, wherein the compound is administered enterally or parenterally.

60. The method of claim 58, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

61. A compound of the formula II



II

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_5 in which R_5 is hydrogen, alkyl, or aryl;
or

R_2 is -CH_2-O-alkyl- (in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1);

R_3 is hydrogen, alkyl, aryl, or aralkyl;

R_4 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_6 in which R_6 is hydrogen, alkyl, aryl, or aralkyl; and

n is 1 to 6;

or a pharmaceutically acceptable acid addition salt thereof.

62. A compound according to claim 61, wherein R_1 is hydrogen.

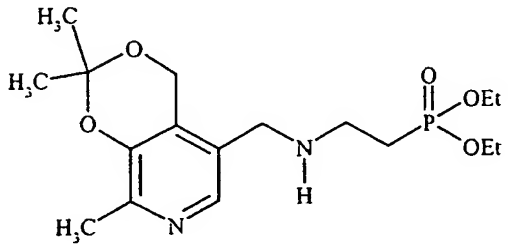
63. A compound according to claim 61, wherein R_2 is $-CH_2OH$, or $-CH_2.O$-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1.

64. A compound according to claim 61, wherein R_3 is hydrogen.

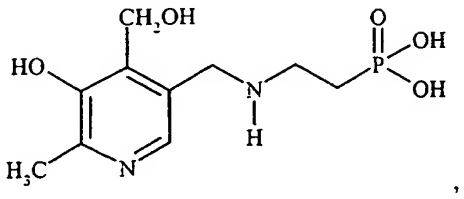
65. A compound according to claim 61, wherein R_4 is alkyl or H.

66. A compound according to claim 65, wherein R_4 is ethyl.

67. A compound according to claim 61 selected from

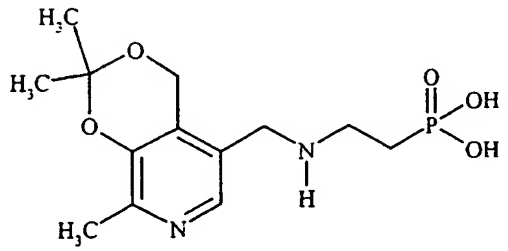


,



,

and



68. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to claim 61.

69. A pharmaceutical composition of claim 68, wherein the pharmaceutical composition is in a form suitable for enteral or parenteral administration.

70. A method of treating hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

71. The method of claim 70, wherein the compound is administered enterally or parenterally.

72. The method of claim 70, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

73. A method of treating myocardial infarction in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

74. The method of claim 73, wherein the compound is administered enterally or parenterally.

75. The method of claim 73, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, an antithromblytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

76. A method of treating ischemia reperfusion injury in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

77. The method of claim 76, wherein the compound is administered enterally or parenterally.

78. The method of claim 76, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

79. A method of treating myocardial ischemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

80. The method of claim 79, wherein the compound is administered enterally or parenterally.

81. The method of claim 79, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

82. A method of treating congestive heart failure in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 55 in a unit dosage form.

83. The method of claim 82, wherein the compound is administered enterally or parenterally.

84. The method of claim 82, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an

angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, and a mixture thereof.

85. A method of treating arrhythmia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

86. The method of claim 85, wherein the compound is administered enterally or parenterally.

87. The method of claim 85, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of a calcium channel blocker, a β-adrenergic receptor antagonist, and a mixture thereof.

88. A method of reducing blood clots in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

89. The method of claim 88, wherein the compound is administered enterally or parenterally.

90. The method of claim 88, wherein the compound is administered concurrently with an antithrombolytic agent.

91. A method of treating hypertrophy in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

92. The method of claim 91, wherein the compound is administered enterally or parenterally.

93. The method of claim 91, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

94. A method of treating a disease that arises from thrombotic and prothrombotic states in which the coagulation cascade is activated in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

95. The method of claim 94, wherein the compound is administered enterally or parenterally.

96. The method of claim 94, wherein the disease comprises deep vein thrombosis.

97. The method of claim 94, wherein the disease comprises disseminated intravascular coagulopathy.

98. The method of claim 94, wherein the disease comprises pulmonary embolism.

99. A method of treating diabetes mellitus in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

100. The method according to claim 99, wherein the diabetes mellitus treated is insulin-dependent diabetes mellitus.

101. The method according to claim 100, wherein the compound is administered concurrently with insulin.

102. The method according to claim 99, wherein the diabetes mellitus treated is noninsulin-dependent diabetes mellitus.

103. The method according to claim 102, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

104. The method according to claim 99, wherein the compound is administered enterally or parenterally.

105. A method of treating insulin resistance in a mammal comprising concurrently administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

106. The method of claim 105, wherein the compound is administered enterally or parenterally.

107. The method of claim 105, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

108. A method of treating hyperinsulinemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

109. The method of claim 108, wherein the compound is administered enterally or parenterally.

110. The method of claim 108, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

111. A method of treating diabetes-induced hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

112. The method of claim 111, wherein the compound is administered enterally or parenterally.

113. The method of claim 111, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

114. A method of treating diabetes-related damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

115. The method of claim 114, wherein the compound is administered enterally or parenterally.

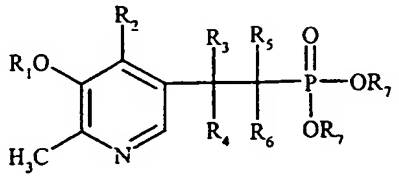
116. The method of claim 114, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

117. A method of treating obesity in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 61 in a unit dosage form.

118. The method of claim 117, wherein the compound is administered enterally or parenterally.

119. The method of claim 117, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

120. A compound of the formula III



III

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_8 in which R_8 is hydrogen, alkyl, or aryl;

or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy or alkylcarbonyloxy; or

R_3 and R_4 can be taken together to form =O;

R_5 and R_6 are hydrogen; or

R_5 and R_6 are halo; and

R_7 is hydrogen, alkyl, aryl, aralkyl, or –CO_2R_8 in which R_8 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable acid addition salt thereof.

121. A compound according to claim 120, wherein R_1 is hydrogen.

122. A compound according to claim 120, wherein R_2 is -CH_2O or -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1.

123. A compound according to claim 120, wherein R_4 is -OH or $CH_3C(O)O$-.

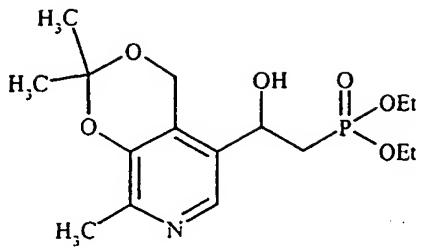
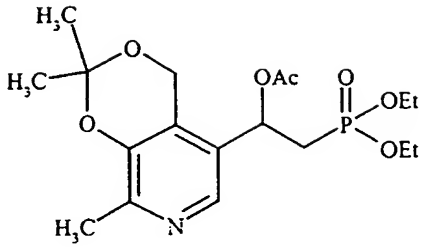
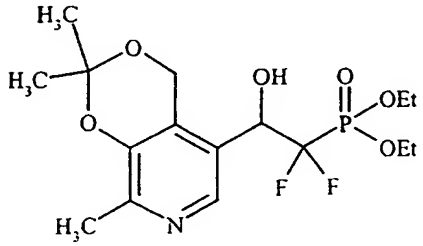
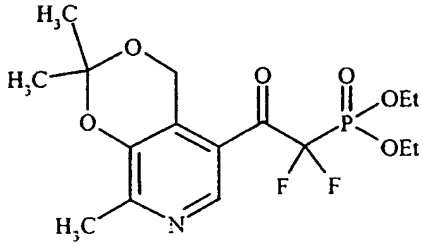
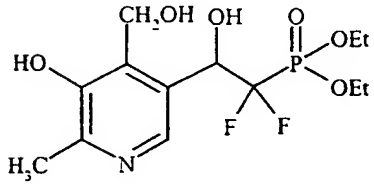
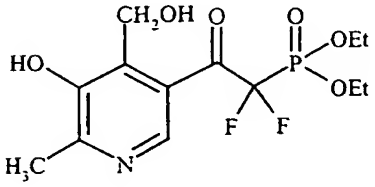
124. A compound according to claim 120, wherein R_3 and R_4 taken together form =O.

125. A compound according to claim 120, wherein R_5 and R_6 are F.

126. A compound according to claim 120, wherein R_7 is alkyl.

127. A compound according to claim 126, wherein R_7 is ethyl.

128. A compound according to claim 120 selected from


,

,

,

,

, and

.

129. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to claim 120.

130. A pharmaceutical composition of claim 129, wherein the pharmaceutical composition is in a form suitable for enteral or parenteral administration.

131. A method of treating hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

132. The method of claim 131, wherein the compound is administered enterally or parenterally.

133. The method of claim 131, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an

angiotensin converting enzyme inhibitor, a calcium channel blocker, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

134. A method of treating myocardial infarction in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

135. The method of claim 134, wherein the compound is administered enterally or parenterally.

136. The method of claim 134, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, an antithromblytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

137. A method of treating ischemia reperfusion injury in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

138. The method of claim 137, wherein the compound is administered enterally or parenterally.

139. The method of claim 137, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

140. A method of treating myocardial ischemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

141. The method of claim 140, wherein the compound is administered enterally or parenterally.

142. The method of claim 140, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

143. A method of treating congestive heart failure in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

144. The method of claim 143, wherein the compound is administered enterally or parenterally.

145. The method of claim 143, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, and a mixture thereof.

146. A method of treating arrhythmia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

147. The method of claim 146, wherein the compound is administered enterally or parenterally.

148. The method of claim 147, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of a calcium channel blocker, a β-adrenergic receptor antagonist, and a mixture thereof.

149. A method of reducing blood clots in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

150. The method of claim 149, wherein the compound is administered enterally or parenterally.

151. The method of claim 149, wherein the compound is administered concurrently with an antithrombolytic agent.

152. A method of treating hypertrophy in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

153. The method of claim 152, wherein the compound is administered enterally or parenterally.

154. The method of claim 152, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

155. A method of treating a disease that arises from thrombotic and prothrombotic states in which the coagulation cascade is activated in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

156. The method of claim 155, wherein the compound is administered enterally or parenterally.

157. The method of claim 155, wherein the disease comprises deep vein thrombosis.

158. The method of claim 155, wherein the disease comprises disseminated intravascular coagulopathy.

159. The method of claim 155, wherein the disease comprises pulmonary embolism.

160. A method of treating diabetes mellitus in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

161. The method according to claim 160, wherein the diabetes mellitus treated is insulin-dependent diabetes mellitus.

162. The method according to claim 161, wherein the compound is administered concurrently with insulin.

163. The method according to claim 160, wherein the diabetes mellitus treated is noninsulin-dependent diabetes mellitus.

164. The method according to claim 163, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

165. The method according to claim 163, wherein the compound is administered enterally or parenterally.

166. A method of treating insulin resistance in a mammal comprising concurrently administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

167. The method of claim 166, wherein the compound is administered enterally or parenterally.

168. The method of claim 166, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

169. A method of treating hyperinsulinemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

170. The method of claim 169, wherein the compound is administered enterally or parenterally.

171. The method of claim 169, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

172. A method of treating diabetes-induced hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

173. The method of claim 172, wherein the compound is administered enterally or parenterally.

174. The method of claim 172, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

175. A method of treating diabetes-related damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

176. The method of claim 175, wherein the compound is administered enterally or parenterally.

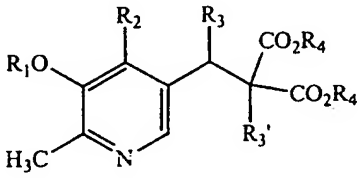
177. The method of claim 175, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

178. A method of treating obesity in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 120 in a unit dosage form.

179. The method of claim 178, wherein the compound is administered enterally or parenterally.

180. The method of claim 178, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

181. A compound of the formula IV



IV

in which

R_1 is hydrogen or alkyl;

R_2 is –CHO, -CH_2OH, -CH_3 or –CO_2R_5 in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is -CH_2.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1;

R_3 and R_3' are independently hydrogen or halo; or

R_3 and R_3' taken together constitute a second covalent bond between the carbons to which they are substituent; and

R_4 is hydrogen or alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

182. A compound of claim 181, wherein R_1 is hydrogen.

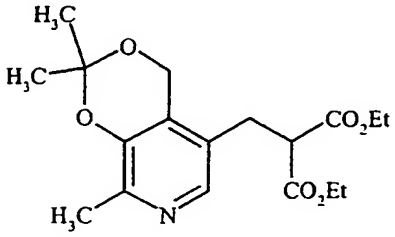
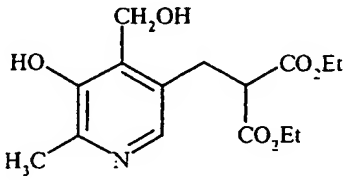
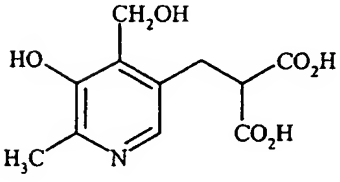
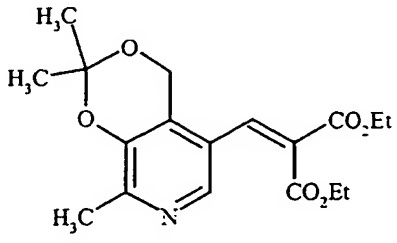
183. A compound of claim 181, wherein R_2 is $-CH_2OH$ or $-CH_2$.O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1.

184. A compound of claim 181, wherein R_3 and R_3' are independently hydrogen or F.

185. A compound of claim 181, wherein R_4 is hydrogen or ethyl.

186. A compound of claim 181, wherein R_3 and R_3' taken together constitute a second covalent bond between the carbons to which they are substituent.

187. A compound according to claim 181 selected from


,

,

, and

.

188. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to claim 181.

189. A pharmaceutical composition of claim 188, wherein the pharmaceutical composition is in a form suitable for enteral or parenteral administration.

190. A method of treating hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

191. The method of claim 190, wherein the compound is administered enterally or parenterally.

192. The method of claim 190, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, a β-adrenergic receptor antagonist, a vasodilator, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

193. A method of treating myocardial infarction in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

194. The method of claim 193, wherein the compound is administered enterally or parenterally.

195. The method of claim 193, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, a calcium channel blocker, an antithromblytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

196. A method of treating ischemia reperfusion injury in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

197. The method of claim 196, wherein the compound is administered enterally or parenterally.

198. The method of claim 196, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

199. A method of treating myocardial ischemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

200. The method of claim 199, wherein the compound is administered enterally or parenterally.

201. The method of claim 199, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, an antithrombolytic agent, a β-adrenergic receptor antagonist, a diuretic, an α-adrenergic receptor antagonist, and a mixture thereof.

202. A method of treating congestive heart failure in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

203. The method of claim 202, wherein the compound is administered enterally or parenterally.

204. The method of claim 202, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an

angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a vasodilator, a diuretic, and a mixture thereof.

205. A method of treating arrhythmia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

206. The method of claim 205, wherein the compound is administered enterally or parenterally.

207. The method of claim 205, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of a calcium channel blocker, a β-adrenergic receptor antagonist, and a mixture thereof.

208. A method of reducing blood clots in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

209. The method of claim 208, wherein the compound is administered enterally or parenterally.

210. The method of claim 208, wherein the compound is administered concurrently with an antithrombolytic agent.

211. A method of treating hypertrophy in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

212. The method of claim 211, wherein the compound is administered enterally or parenterally.

213. The method of claim 211, wherein the compound is administered concurrently with a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, and a mixture thereof.

214. A method of treating a disease that arises from thrombotic and prothrombotic states in which the coagulation cascade is activated in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

215. The method of claim 214, wherein the compound is administered enterally or parenterally.

216. The method of claim 214, wherein the disease comprises deep vein thrombosis.

217. The method of claim 214, wherein the disease comprises disseminated intravascular coagulopathy.

218. The method of claim 214, wherein the disease comprises pulmonary embolism.

219. A method of treating diabetes mellitus in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

220. The method according to claim 219, wherein the diabetes mellitus treated is insulin-dependent diabetes mellitus.

221. The method according to claim 219, wherein the compound is administered concurrently with insulin.

222. The method according to claim 219, wherein the diabetes mellitus treated is noninsulin-dependent diabetes mellitus.

223. The method according to claim 222, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

224. The method according to claim 219, wherein the compound is administered enterally or parenterally.

225. A method of treating insulin resistance in a mammal comprising concurrently administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

226. The method of claim 225, wherein the compound is administered enterally or parenterally.

227. The method of claim 225, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

228. A method of treating hyperinsulinemia in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

229. The method of claim 228, wherein the compound is administered enterally or parenterally.

230. The method of claim 228, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

231. A method of treating diabetes-induced hypertension in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

232. The method of claim 231, wherein the compound is administered enterally or parenterally.

233. The method of claim 231, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

234. A method of treating diabetes-related damage to blood vessels, eyes, kidneys, nerves, autonomic nervous system, skin, connective tissue, or immune system in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

235. The method of claim 234, wherein the compound is administered enterally or parenterally.

236. The method of claim 234, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

237. A method of treating obesity in a mammal comprising administering to the mammal a therapeutically effective amount of a compound according to claim 181 in a unit dosage form.

238. The method of claim 237, wherein the compound is administered enterally or parenterally.

239. The method of claim 237, wherein the compound is administered concurrently with insulin or a hypoglycemic compound.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00265

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/58 C07D213/65 C07D213/66 A61K31/44 A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TOMITA ET AL: "Synthesis of Vitamin B6 Derivatives. II. 3-Hydroxy-4-Hydroxymethyl-2-Methyl-5-Pyridine Acetic Acid and Related Substances" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 3, 1966, pages 178-183, XP001000584 ISSN: 0022-152X * Compounds Xa and XIa * ---	181-185, 187
X	US 4 696 920 A (BENTZEN CRAIG L ET AL) 29 September 1987 (1987-09-29) example 21 --- -/--	181, 183-185, 187

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2001	06/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Elliott, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00265

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KORYTNYK: "Pyridoxine Chemistry. VI. Homologs of Pyridoxol and of 5-Pyridoxic Acid" JOURNAL OF MEDICINAL CHEMISTRY, vol. 8, January 1965 (1965-01), pages 112-115, XP001000642 ISSN: 0022-2623 * Compound II *	181,183, 185,186
A	KORYTNYK ET AL: "Synthesis and Antagonist Properties of Pyridoxal Analogs Modified in the 5 Position" JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 2, 1967, pages 345-350, XP001000527 ISSN: 0022-2623 * Compound XXXII *	181-239
A	MARGARET L. FONDA: "Interaction of Pyridoxal Analogues with Glutamate Apodecarboxylase and Aspartate Apoaminotransferase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 246, no. 7, 10 April 1971 (1971-04-10), pages 2230-2240, XP002170146 ISSN: 0021-9258 table III	1-60, 180-239
A	YAN ET AL: "A Role for Pyridoxal Phosphate in the Control of Dephosphorylation of Phosphorylase a" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 254, no. 17, 10 September 1979 (1979-09-10), pages 8263-8269, XP001000732 ISSN: 0021-9258 table II	1-60, 120-239
A	KIM ET AL: "Synthesis and Structure-Activity Realtonships of Pyridoxal-6-arylazo-5'-phosphate and Phosphonate Derivatives as P2 Receptor Antagonists" DRUG DEVELOPMENT RESEARCH, vol. 45, no. 2, 1998, pages 52-66, XP002170147 ISSN: 0272-4391 * Compounds 19,22,26,28,37,38,39 on page 61 *	1-60, 120-180

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir .ational Application No
PCT/CA 01/00265

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BENNETT ET AL: "Vitamin B6 Phosphonic Acids" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, vol. 1, no. 3, 1959, pages 213-221, XP001000566 ISSN: 0095-9065 * see whole document * ---	1-60
A	WO 98 28310 A (BENTZEN CRAIG LEIGH ;DIEP VINH VAN (CH); NIESOR ERIC (CH); AZOULAY) 2 July 1998 (1998-07-02) * see whole document * ---	61-119
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 11, 30 September 1998 (1998-09-30) -& JP 10 158244 A (KISSEI PHARMACEUT CO LTD), 16 June 1998 (1998-06-16) abstract ---	61-119
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ARBUZOV, S. YA.: "Synthesis and pharmacological investigation of some new compounds related structurally to some natural metabolites" retrieved from STN Database accession no. 72:20229 XP002170149 abstract & CONF. HUNG. THER. INVEST. PHARMACOL., SOC. PHARMACOL. HUNG., 4TH (1968), MEETING DATE 1966, 489-502. EDITOR(S): DUMBOVICH, B. PUBLISHER: AKAD. KIADO, BUDAPEST, HUNG. , ---	61-119
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ARBUZOV, S. YA.: "Pharmacological properties of the products of the condensation of phenamine with some metabolites" retrieved from STN Database accession no. 69:58274 XP002170150 abstract & FARMAKOL. TOKSIKOL. (1968), 31(3), 373-6 , --- -/--	61-119

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00265

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EBADI ET AL: "Convulsant activity of pyridoxal sulphate and phosphonoethyl pyridoxal: antagonism by GABA and its synthetic analogues" NEUROPHARMACOLOGY, vol. 22, no. 7, January 1983 (1983-01), pages 865-873, XP001000735 ISSN: 0028-3908 page 867 ---	120-239
A	MIURA ET AL: "Reactions of Phosphonate Analogs of Pyridoxal Phosphate with Apo-aspartate Aminotransferase" ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 270, no. 2, 1 May 1989 (1989-05-01), pages 526-540, XP001000748 ISSN: 0003-9861 * Compounds II-V * ---	120-239
A	STIRTAN ET AL: "Phosphonate and alpha-Fluorophosphonate Analogue Probes of the Ionization State of Pyridoxal 5'-Phosphate (PLP) in Glycogen Phosphorylase" BIOCHEMISTRY, vol. 35, no. 47, 1996, pages 15057-15064, XP002170148 ISSN: 0006-2960 * Chart 1 on page 15059 * ---	120-180
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 04, 31 August 2000 (2000-08-31) -& JP 2000 026295 A (UNIV MANITOBA), 25 January 2000 (2000-01-25) cited in the application abstract	1-239
P,A	-& US 6 043 259 A (DHALLA ET AL) 28 March 2000 (2000-03-28) cited in the application ---	
A	WO 99 53928 A (UNIV MANITOBA ;MEDICURE INC (CA)) 28 October 1999 (1999-10-28) cited in the application the whole document -----	1-239

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 01/00265

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4696920 A	29-09-1987	CH 664158 A	15-02-1988
		AT 38991 T	15-12-1988
		AU 581442 B	23-02-1989
		AU 4511485 A	23-01-1986
		CA 1284320 A	21-05-1991
		CS 8505305 A	15-07-1988
		DE 3566545 D	05-01-1989
		DE 173041 T	12-06-1986
		DK 324185 A	19-01-1986
		EP 0173041 A	05-03-1986
		ES 545330 D	16-12-1986
		ES 8702427 A	16-03-1987
		FI 852806 A,B,	19-01-1986
		GR 851767 A	26-11-1985
		HU 38950 A,B	28-07-1986
		IL 75807 A	10-09-1989
		JP 61040294 A	26-02-1986
		KR 9305390 B	19-06-1993
		NO 852822 A	20-01-1986
		NZ 212768 A	30-06-1988
		PT 80820 A,B	01-08-1985
		SU 1375141 A	15-02-1988
		YU 117185 A	31-10-1987
		ZA 8505357 A	26-02-1986
WO 9828310 A	02-07-1998	AU 5858898 A	17-07-1998
		BG 103574 A	30-11-2000
		BR 9714650 A	03-10-2000
		EP 0946572 A	06-10-1999
		HU 0002171 A	28-05-2001
		NO 993001 A	18-06-1999
		PL 334189 A	14-02-2000
		SK 81099 A	08-11-1999
		TR 9901423 T	21-10-1999
		ZA 9711431 A	21-06-1999
JP 10158244 A	16-06-1998	NONE	
JP 2000026295 A	25-01-2000	AU 9421098 A	03-02-2000
		US 6043259 A	28-03-2000
WO 9953928 A	28-10-1999	US 6051587 A	18-04-2000
		AU 3402999 A	08-11-1999
		EP 1071430 A	31-01-2001